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Titers of Gonadotrophins in Urine of Aged Eunuchs[1]

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THE TITERS of urinary gonadotrophins excreted by aging men who had been eunuchs since childhood were measured and compared with those excreted by normal, old men. Collateral studies were directed toward ascertaining whether the excretion of large quantities of urinary gonadotrophins by these eunuchs, and the correlated condition of heightened secretory function of the pituitary gland, had continued through the extended period of time during which these men had been castrate, an interval of as much as half a century of life.

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MATERIALS AND METHODS

The subjects consisted of the following:

Four eunuchs (*Cases 1–4*) who had been castrated between the eighth and twelfth years of life and at the time of examination were 53, 54, 54, and 63 years of age, respectively (Table 1). The time that had elapsed between orchiectomy and the present study of these men amounted to 44, 45, 45, and 51 years. *Cases 1* and *2* are brothers.

Ten non-castrated males (*Cases 5–14*) in good health, who were between 55 and 76 years of age, served as controls for the above cases (Table 1). These men were selected at random from inmates of a home for aged persons.

Data available for comparison with those from eunuchs castrated before puberty have been obtained for men who were castrated after attaining puberty. Such studies have been published elsewhere (15, 16), and include titers of urinary gonadotrophins, androgens and estrogens (1, 18).

TABLE 1

Case	Age in years			Urinary gonadotrophins	
	At castration	At examination	After castration	No. of days	Aver. in M.U. per 24 hours
Eunuchs castrated *before* puberty					
1	8	53	45	2	160
2	9	54	45	2	160
3	10	54	44	2	40
4	12	63	51	2	>40
				2	>40
					<80
Eunuchs castrated *when mature*[2]					
I.H.	43	56	13	6	55
H.F.	19	45	26	8	62
G.S.	23	43	20	16	77
M.G.	41	43	2	4	30
C.S.	26	39	13	12	32
H.M.	35	36	1	14	110
Normal *old* men					
5		72		3	17
6		76		3	10–14
7–14		55–65		3–6	7–25
Normal *young* men[3]					
N.V.		23		96	8
N.J.		22		104	11
N.D.		33		180	12
N.H.		21		132	15
N.S.		24		32	25

[2] Previously published data (Catchpole and associates, 1942).
[3] Data obtained by Werner (1943).

For assay of gonadotrophic substances, urine was collected from all subjects for two or more periods of 24 consecutive hours. Extractions of gonadotrophins from the urine of the first group were made by Zondek's method (48) of precipitation with alcohol. This is a relatively simple technique that could be carried out at the patients' hospitals, and thus obviate the necessity for shipment of urine over long distances. The method of Freed and Hechter (10) was used in extraction of gonadotrophic substances from the urine of the other subjects, the normal men referred to here and the men castrated after puberty as reported by Catchpole and associates (1, 12). The procedure employed in the bio-assay in all instances has been described in detail elsewhere by Catchpole (12). Values for gonadotrophins are expressed in mouse units (M.U.). One M.U. is defined as the amount of hormone that under standard conditions doubles the ratio of uterine weight/body weight in 21–23 day old female mice, which have been given six injections of the test-substances in from 36 to 40 hours. The animals were sacrificed at 72 hours, and the uterine and body weights were measured by the procedure outlined by Levin and Tyndale (29), modified by Catchpole (12). One M.U. is equivalent to the response obtained with 0.1 I.U. of equine gonadotrophin.

RESULTS AND DISCUSSION

Values for urinary gonadotrophins in normal men and in old eunuchs who had been castrated before attaining sexual maturity.

In old eunuchs who had been castrated before puberty, the excretion of urinary gonadotrophins (Table 1) was unquestionably supranormal in *Cases 1* and *2* (160 and 160 M.U.), and in all probability also in *Cases 3* and *4* (40 and >40 – <80 M.U.). The titers for these four subjects are in the same range as the average values of 30–110 M.U. found in cases in which the removal or destruction of the testes occurred after maturity (Table 1)

The average quantities of urinary gonadotrophins excreted by the normal old men are similar to those of young men (Table 1). The values for the oldest men, *Cases 5* and *6*, are from 10 to 17 M.U. daily. Those for *Cases 7* and *14* are from 7 to 25 M.U. and are reported together inasmuch as they are essentially alike, and it has been shown previously in

other and more extensive studies by Heller and associates (22) that with increase in age normal men do not excrete large quantities of urinary gonadotrophins.

Included in Table 1, to facilitate comparisons, are Werner's (44) measurements of the amount of gonadotrophins in 48 hour specimens of urine collected for a month or more from normal men. The titers never exceeded 20 M.U. in subject *N.V.* during 96 days, or in *N.J.* during 104 days. Values of 40 M.U. were attained in two of 90 samples (180 days) from *N.D.*, were exceeded in seven of 66 samples (132 days) from *N.H.* and in three of 16 samples (32 days) from *N.S.*

The excretion of greater than average amounts of urinary gonadotrophins by eunuchs is to be attributed not to age or technical procedures but to the effects of castration (8, 13, 14). Errors in technique which would cause undetected destruction of urinary gonadotrophins would result in a decrease rather than an increase of values. There seems to be no possibility that the values are scaled high, because the assays were checked against standardized amounts of equine gonadotrophin and because abnormally high measurements were not obtained with our use of these methods in studies of a variety of other persons: specifically, children (12), normal men (see above), and patients with eunuchoidism or certain types of dwarfism (unpublished data).

The elevated titers of urinary gonadotrophins in castrates reflect the augmented function of the pituitary gland that results when gonadal secretions are reduced (14, 38). In animals the gonadotrophic content, and in some instances the secretory activity, of the anterior lobe of the pituitary gland have been shown to be increased following castration. This has been demonstrated for rats (6, 7), mice (30), guinea pigs (26, 37), and horses (20). The augmented production of gonadotrophins in castrated animals can be prevented to a large degree by the administration of substances similar to gonadal secretions, either estrogens (25, 26, 32–24), or androgens (19, 21, 24, 25). Similarly, the high titers of urinary gonadotrophins in eunuchs are reduced upon treatment of these men with androgens (1).

Evidence suggesting that the castrates, Cases 1–4, have continued to excrete large quantities of gonadotrophins since at least the chronological age for puberty, an interval of more than 40 years in three cases and approximately 50 years in a fourth.

In collateral studies the amounts of urinary gonadotrophins excreted by castrate boys have been found to be elevated at the normal chronological age of puberty. In a boy who was studied both before and after bilateral orchiectomy, performed when he was 15 years old and in an early stage of puberty (Stage III as described by Greulich and associates (12)), the average daily excretion of urinary gonadotrophins amounted to less than 3.5 M.U. before castration, but increased to 50 M.U. within four weeks after orchiectomy. The amounts of urinary gonadotrophins were similarly increased immediately following the castration of two other boys, 14 and 13 years old, respectively (unpublished data of the present authors) and were found to be high in a 12 year old eunuch mentioned by Hamburger (14). The high titers must be attributed to the effects of castration. Not only do the average values for these young eunuchs surpass the range of such figures for normal adult men but the rapidity of the increase in titers far exceeds that observed during normal puberty (12, 35). In view of the fact that in all four of the instances in which studies have been made, castration early in life led to abnormally high titers of urinary gonadotrophins at or before the usual chronological ages of puberty, it seems likely that the patients (*Cases 1–4*) who had also been castrated before puberty began to excrete supranormal quantities of urinary gonadotrophins during or even prior to the usual age of puberty. Since eunuchs continue to excrete these excessively large amounts of gonadotrophins during the middle years of life (1, 13, 14), it appears that old men who have been castrated before puberty may excrete large amounts of these substances for many years;

This state has persisted in three cases for over 40 years and in another for 50 years or more.

Effects of this apparently prolonged state of hyperfunction of the anterior lobe of the pituitary gland.

For the reasons given above, the greatly increased amounts of urinary gonadotrophins in castrated individuals may be presumed with a considerable degree of assurance to be a reflection of the secretion of large quantities of gonadotrophins by the anterior lobe of the pituitary gland. Continuation of this state in eunuchs for nearly half a century of life is an outstanding example of long continued hyperfunction by an endocrine gland. It suggests that "exhaustion" of the pituitary gland as a result of treatment with estrogens (9) does not arise simply from excessive activity. It also raises a question as to the influence of such prolonged and excessive function upon tumorigenesis of the gland itself and upon the responses of other parts of the body.

Attempts to evaluate the relation of continued hyperfunction to tumorigenesis of the anterior lobe of the pituitary gland lie beyond the scope of this paper. However, as will be discussed in detail elsewhere, the presence of tumors in any of the 150 eunuchs, more than 60 of whom have been castrated for longer than ten years, was not indicated by any obvious symptoms such as headaches. Neither was there any bitemporal reduction of visual fields in studies of 24 cases, nor enlargement or erosion of the sella turcica in the roentgenographic studies of six men who had been orchiectomized for more than 40 years. These clinical studies have been difficult to carry out as completely as desirable, because the patients are feeble-minded and, until recently, autopsies could not be obtained.

None of this series of 150 eunuchs showed evidence of an abnormal skeletal configuration that might be considered to be associated in any way with excessive function or tumors of the pituitary gland. An appearance suggestive of acromegaly was noted in two of 50 other eunuchs who were not sufficiently cooperative to permit detailed study. These two cases were brothers, 30 and 32 years of age, each of whom had been castrated when 22 years old. The diagnosis of acromegaly was suggested by the appearance of the hands and face. The further course of these two patients is being followed with considerable interest, since acromegaloid signs have been described, but without emphasis, in two of ten Caucasian eunuchs (27), in one of 12 other cases (31), in one of 11 Negro castrates (41), and in one of 31 Chinese eunuchs (42).

Roentgenographic examination of the sella turcica of *Cases 1–4* and of two other eunuchs who had been castrated for more than 40 years showed, as was the case in the Caucasian and Chinese eunuchs studied by Tandler and Gross (40) and Wagenseil (1933) that this structure, although large in some instances, did not exceed the normal range of size. A sella turcica slightly larger than that considered as the normal is not pathognomonic of a tumor of the pituitary gland, and, in fact, a tumor of eosinophilic cells is not present in all cases of acromegaly (2).

In rare instances eunuchs have well developed secondary sexual characters, and they also excrete urinary steroids in a quantity and of a type that suggest the development of a state analogous to that seen in castrated guinea pigs and mice which have developed hyperfunction and tumorous tendencies of the adrenal glands (39, 46, 47). In a series of 220 eunuchs three such instances have been described (17), including one case with advanced gynecomastia and high titers of urinary steroid compounds. After Doctor Konrad Dobriner and his co-workers isolated these steroids, an unusually large proportion was identified as compounds believed to be derived from the cortices of the adrenal glands.

Thus, certain individuals following castration may exhibit either signs of an increased function of the pituitary gland in the form of acromegaly, or such development of the secondary sex characters and pattern of urinary steroids as to be suggestive of increased function of the cortices of the adrenal glands. It would seem that parallel with the increased secretion of gonadotrophins by the pituitary

gland there may be a tendency to enhancement of hypophyseal functions such as those which pertain to growth or to stimulation of certain functions of the adrenal cortex. The limited number of types of cells in the anterior lobe of the pituitary gland might be interpreted to support the belief that an increase in one of the secretions by this gland might involve changes also in some of the many other secretory products attributed to these same cells. The occurrence of other effects in addition to an increased production of gonadotrophins may depend upon the particular genetic background of the individual. An abnormal adrenal function occurs in only certain strains of castrate mice.

Evidence that a climacteric-like state does not ensue normally in aging men.

The above and other data (1, 14), show that the titers of urinary gonadotrophins become elevated in the majority although not in all instances in which testicular function ceases, whether the cessation occurs early or late in life. It is noteworthy, therefore, that none of the ten non-castrated old men exhibited the high values for urinary gonadotrophins that characterize primary failure of gonadal secretion. In a study by Heller and colleagues (22) the titers of urinary gonadotrophins in 21 normal men aged 50 or more did not exceed those in 20 normal men less than 50 years old. The results reported by Heller and associates (22), although not defined in M.U. or with reference to other standards that we can compare directly with our figures, indicate a similar failure of men normally to develop a state of testicular insufficiency.

In a later study Heller and Myers (23) described as "climacteric" 23 of an unstated number of men having varied complaints of a psychoneurotic character. The classification was based partly on clinical signs and symptoms, histologic appearance of a testicular biopsy, and the response to androgenic treatment, but chiefly on the presence of high titers of urinary gonadotrophins. Apparently only a single morning sample of urine from each person was assayed, a procedure which is scarcely quantitative and does not take into account sporadic increases in titers known to occur in normal men (44). Nevertheless, in conjunction with the findings of Witschi and Riley (45) that the gonadotrophic content of the pituitary gland tends to be higher in a few men of 45 or more years of age, these facts suggest that titers of urinary gonadotrophins may be expected to be high in an undetermined but probably small percentage of old men. The crucial points which remain to be ascertained are to what degree these high titers of gonadotrophins of some old men reflect the day-to-day status of the individual, and if they indicate a change from conditions present in young men. It is to be hoped that future studies of the endocrine status of aging men will center on matters capable of quantitative measurement, such as values for hormones in bodily tissues and fluids and not revolve about the presence or absence of subjective symptoms.

It is concluded, therefore, that a primary gonadal insufficiency similar to that which occurs in women can also occur in aging males as a result of bilateral orchiectomy or destruction of the testes, but that climacteric-like states do not occur in a restricted range of age and do not appear to be the usual or normal sequelae of age in men. The present report stands in contrast to claims (3–5, 11, 28, 43) that upon aging men undergo climacteric-like states. It might be suggested that the term primary testicular insufficiency would accurately describe cases with failure of testicular secretions and high titers of urinary gonadotrophins; yet at the same time it would lack the implication introduced by the word, climacteric, that an abrupt, terminal, and more or less normal change has occurred.

The fact that the quantities of urinary gonadotrophins of these old men are within and not below the range characteristic of young adults suggests that with aging there is no major decrease in the degree of gonadotrophic stimulation afforded the testes.

SUMMARY

Four men, who had been castrated when

they were from eight to twelve years of age, and who at the time of the present study had been eunuchs for from 44 to 51 years, excreted large quantities of urinary gonadotrophins. The average daily amounts in M.U. were, respectively, 160, 160, 40, and between 40 and 80. The range of these values is comparable to the supranormal titers generally found subsequent to the castration of mature men (Table 1). It far exceeds the average quantity of urinary gonadotrophins, amounting to 10–25 M.U., excreted daily by ten normal men aged 55 to 76 years.

The presence of large amounts of gonadotrophins in the urine of eunuchs castrated before puberty seems to date from the normal chronological age of puberty, if not slightly earlier, as judged by collateral studies of four boys who were castrated before they matured sexually. This fact, and previously reported findings that eunuchs continue to excrete supranormal amounts of gonadotrophins during adult life, make it appear very probable that large quantities of urinary gonadotrophins have been excreted by three of these eunuchs for over 40 years and by a fourth for about 50 years.

Since in all probability the elevated titers of gonadotrophins in castrate individuals reflect an augmented secretion of gonadotrophins by the pituitary gland, a continued production of greatly supranormal quantities of gonadotrophins during most of the life of these eunuchs, approximately half a century in *Case 4*, provides a striking illustration of the prolonged hyperfunction of an endocrine gland. Incomplete evidence suggests that in some castrates an abnormal function of the pituitary gland may involve more than the production of exceptionally large amounts of gonadotrophins.

The quantity of urinary gonadotrophins of all the normal old men studied was within the range reported for normal young men, a strong indication that none of the old men had developed a climacteric state of gonadal insufficiency or was lacking in gonadotrophic stimulation of the testes. Although primary gonadal insufficiency does occur in old men, as after bilateral orchiectomy or destructon of the testes, it is concluded that climacteric conditions comparable to those in women do not occur in a restricted range of age and do not appear to be the usual or normal sequelae of aging in men.

Table 1 lists the average daily excretion of urinary gonadotrophic substances by four old eunuchs who had been castrated since childhood and by ten non-castrated old men in good health. For comparative purposes data from the literature are listed for normal young men and for eunuchs castrated only after attaining sexual maturation. It is apparent that quantities of urinary gonadotrophins that are materially in excess of the average for normal men characterize castrate men regardless of whether (1) orchiectomy is carried out before or after puberty, or (2 the period of time after castration is brief or prolonged.

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Antithyroid Drugs: I. Tetramethylthiourea and Diethylthiourea[1]

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THE RESULTS obtained by many investigators[2] in the treatment of thyrotoxicosis with thiouracil have indicated that this drug is of distinct aid in controlling the thyrotoxicity regardless of whether the thiouracil constituted the only specific treatment or whether it was used in the preparation of these patients for thyroidectomy. However, the frequency and the nature of the toxic reactions to thiouracil, especially its tendency to produce agranulocytosis, have prompted an investigation of other antithyroid drugs. Since thiouracil, like most of the other agranulocytogenic drugs, has a ring structure, it seemed desirable to investigate the thiourylene substances which have an aliphatic structure. In a study of rats treated with many substances of this type tetramethylthiourea was found to be quite goitrogenic. Diethylthiourea has also been shown (1) to have a distinct goitrogenic effect. In this present paper is presented the results of studies using tetramethylthiourea and diethylthiourea in both man and rats.

TETRAMETHYLTHIOUREA

Physical Properties: Tetramethylthiourea[3] is a white, crystalline powder with a characteristic, inoffensive odor and a bitter taste. At 37° C. one gram of tetramethylthiourea is soluble in 60 cc. of water. Therefore, it is many times more soluble than thiouracil (6). An aqueous solution of tetramethylthiourea kept at a temperature of 5° C. was stable for more than 4 months.

Method of Determination: Estimations[4] of the concentrations of tetramethylthiourea in tissues and body fluids were conducted with methods used in similar studies with thiouracil (3, 6, 7) and thiourea (5). The maximal color reaction of tetramethylthiourea and Grote's reagent occurred within 15 minutes, and remained stable for more than two hours. The color produced was shown by the Hardy recording spectrophotometer to have a maximal absorption of light over the range of 570 to 620 mμ. In the estimations that are reported below a 620 mμ filter and a No. 6 diaphragm were used. Tetramethylthiourea, like thiourea (5), thiouracil (6), and diethylthiourea, was found to combine with proteins of the erythrocytes and leucocytes; consequently, in the estimation of its content in whole blood tryptic digestion was necessary. However, in the determination of the amount of drug in the serum the digestion was not indicated.

In order to ascertain the accuracy of this colorimetric test in the estimation of tetramethylthiourea a number of recovery experiments were conducted. When tetramethylthiourea was added to seven specimens of

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[1] Aided in part by a grant from the Milton Fund of Harvard University.

[2] Many of the reports were referred to in a recent review (2), and a number of others have appeared subsequently. In this clinic we have used thiouracil in the treatment of approximately 240 patients with thyrotoxicosis.

[3] We are indebted to Dr. R. O. Roblin of the American Cyanamide Company, Stamford, Connecticut, for the supply of tetramethylthiourea.

[4] The author is indebted to Miss Gloria Kay for the chemical determinations.

whole blood in quantities sufficient to make concentrations varying from 0.4 to 10 mg. per 100 cc., by the colorimetric test there was demonstrated from 88 to 100 per cent, with an average of 96 per cent. When the drug was added to 11 fine aqueous suspensions of muscle to make concentrations of from 0.4 to 100 mg. per 100 cc., from 94 to 100 per cent, average of 96 per cent, was recovered. With five concentrations, varying from 2 to 10 mg. per 100 cc., 100 per cent of the tetramethylthiourea was identified in the urine.

Pharmacology

1. *Studies with Rats.* The goitrogenic effect of tetramethylthiourea was studied. When this substance was given in the drinking water of Wistar rats in concentrations varying from 0.001 to 0.1 per cent, within 14 days a well defined goitrogenic effect was observed in the animals that received concentrations of 0.04 per cent or greater. The weights of the thyroid glands of the rats receiving tetramethylthiourea were similar to those of a comparable group of animals, treated with equivalent concentrations of sodium thiouracil (Table 1). However, there tended to be more hyperplasia of the thyroid cells in the rats treated with thiouracil. Aside from the changes in the thyroid, no abnormalities were observed on gross examination of the viscera of 12 rats and there were no changes noted in the microscopic sections of the kidneys, liver, spleen, adrenals, pancreas, testes, and bone marrow of three animals treated with 0.1 per cent of tetramethylthiourea for two weeks. All of the rats gained weight relatively well and appeared healthy while taking the drug.

The concentrations of tetramethylthiourea in the blood and the thyroid tissue of rats were compared with those of thiouracil following the treatment of rats with these substances. These drugs were administered in a concentration of 0.1 per cent in the water of three equally divided series of litter mates, there being four rats in each of the six groups. After the animals had been treated for two weeks, blood was withdrawn from the aorta, using ether anaesthesia. They were then killed by a blow on the head, and the thyroid gland was removed. As seen in Table II, the concentrations of tetramethylthiourea in the blood and thyroid tissue were higher than those treated with thiouracil.

2. *Studies with Patients.* In thyrotoxic patients and in normal individuals it was found that tetramethylthiourea, like thiouracil and thiourea, was rapidly absorbed from the gastro-intestinal tract. Individuals who had

TABLE 1

No. of rats	Average weight of rats gm.		Concentration of drug in water per cent	Total volume ingested		Average weight of thyroid mg./100 gm.	
	Tu.*	Tm.		Tu.	Tm.	Tu.	Tm.
8	70	70	0.1			17.6	18.3
6	74	78	0.1	445	385	17.2	16.9
6	70	73	0.05	450	445	13.2	11.0
6	88	89	0.04	510	640	14.1	11.9
6	71	67	0.01	440	385	8.5	8.7
6	89	106	0.01	650	555	8.2	7.0
6	80	89	0.005	580	590	5.8	5.9
6	81	91	0.001	580	590	5.2	5.9

* Tu.—thiouracil; Tm.—tetramethylthiourea.

TABLE 2. CONCENTRATION OF THIOURACIL (TU.) AND TETRAMETHYLTHIOUREA (TM.) IN THE BLOOD AND THYROID TISSUE OF RATS

Series	Blood mg./100 cc.		Thyroid Tissue mg./100 gm. (dry weight)	
	Tu.	Tm.	Tu.	Tm.
1	4.0	6.2	14.6	20.4
2	3.6	7.0	10.6	19.8
3	3.2	5.8	—	—

2. *Studies with Patients.* In thyrotoxic patients and in normal individuals it was found that tetramethylthiourea, like thiouracil and thiourea, was rapidly absorbed from the gastro-intestinal tract. Individuals who had

received tetramethylthiourea in regular doses for several days, for example, 0.2 gm. three times daily, were found to have a higher concentration of this drug in the blood than did individuals receiving thiouracil in like manner (Fig. 1). In these subjects a distinctly smaller proportion of tetramethylthiourea

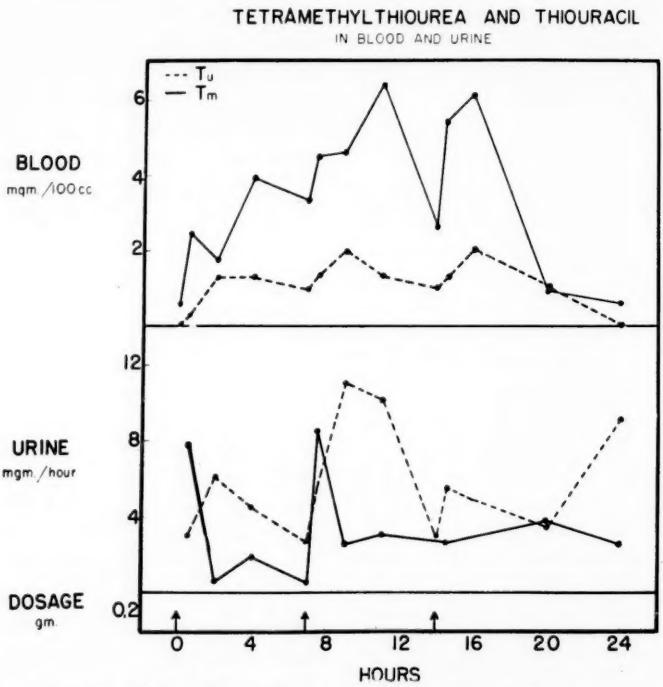

FIG. 1. Note that the patient who had received tetramethylthiourea for several days, in doses of 0.2 gm. three times daily, had a higher concentration of the drug in the blood and a smaller total quantity in the urine than was true in the patient receiving the same amount of thiouracil.

was excreted in the urine (Fig. 1), but, as was true of thiouracil, none was excreted in the stools.

TREATMENT OF THYROTOXIC PATIENTS

1. *Type of Patient.* Thirty patients with thyrotoxicosis were treated with tetramethylthiourea. There were 26 female patients and four male; their ages ranged from 19 to 62 years. Seven had previously been subjected to subtotal thyroidectomy. Seven of the 30 patients had been treated with thiouracil for intervals of from two to 15 months but had experienced a recurrence of the disease on cessation of thiouracil treatment. Three had been treated with iodide within a few weeks preceding therapy with tetramethylthiourea. The thyroid glands of the 30 patients varied in size from 1.5 to 4.5 times normal size; four were adenomatous glands. Three patients had malignant exophthalmos and one had thyrotoxic myopathy. Two subjects were thyrocardiacs and had congestive heart failure.

2. *Outline of Treatment.* Most of the patients were given 0.2 mg. of tetramethylthiourea at eight hour intervals until the basal metabolic rate had become essentially normal. However, three patients were given 0.8 to 1.0 gm. daily for from two to four weeks to observe whether any toxic effects would be produced. Because of the limited supply of tetramethylthiourea most of the patients were treated with thiouracil soon after the

basal metabolic rate had become normal. However, in six of the 13 patients in whom a thyroidectomy was performed no thiouracil was given. For about two weeks preceding thyroidectomy a saturated solution of potassium iodide was prescribed in doses of five drops three times daily. Almost all of the patients were given from four to six capsules of crude liver extract daily, each capsule containing 0.5 gm. of liver powder with 0.40 mg. of the *L. Casei* factor. Three patients who received prolonged treatment with tetramethylthiourea required only 0.2 or 0.1 gm. per day as a maintenance daily dosage. Twenty of the patients were hospitalized during most of the tetramethylthiourea therapy. The other patients were seen at weekly intervals. Special attention was given to the effects of tetramethylthiourea on the thyrotoxicosis, the thyroid gland, the eyes and the basal metabolic rate. A careful watch was kept for toxic reactions to the drug. Leucocyte counts were made on the blood of the hospitalized patients at intervals of from one to three days. Differential blood counts, hemoglobin estimations, and urine examinations were performed about once per week. In eight patients changes in the carbon dioxide combining power, serum chloride, non-protein nitrogen and cholesterol were looked for.

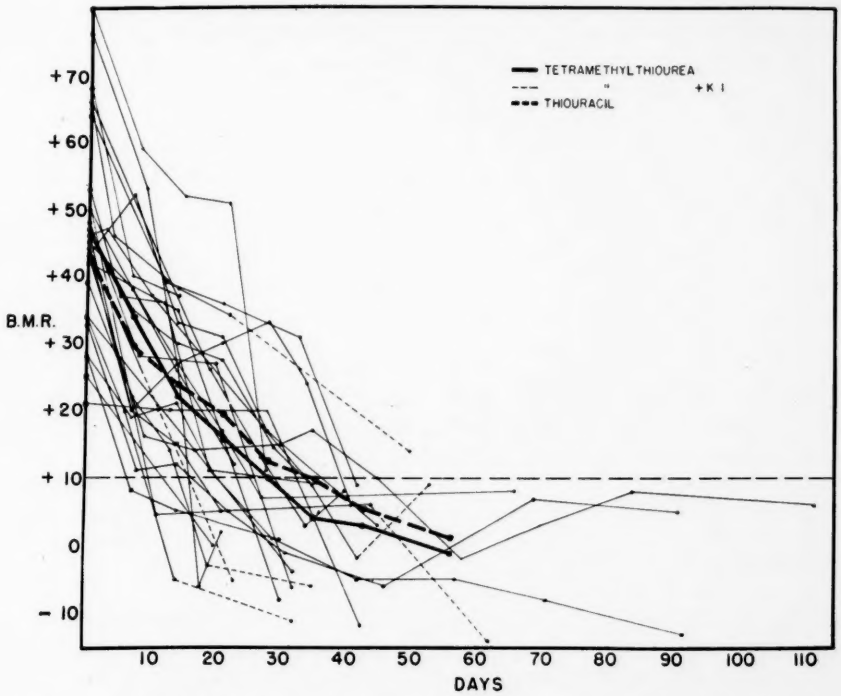

FIG. 2. The broad broken line is the average response in the basal metabolic rate in 152 patients treated with thiouracil (4). The uninterrupted heavy line is the average response of the patients treated with tetramethylthiourea. The thin broken lines represent an interval when potassium iodide was given with tetramethylthiourea. The former was used to bring about some involution of the thyroid gland in preparation of the patient for thyroidectomy. The proportion of patients kept in the hospital was larger for those treated with tetramethylthiourea than for those treated with thiouracil.

3. *Response in the Disease.* The response was similar to that following thiouracil treatment reported by many investigators. The thyrotoxic manifestations began to subside within a few days after starting treatment and after from four to six weeks they had largely or entirely disappeared. The thyroid gland did not change appreciably in size, al-

though in some instances it became a little smaller and in a few it became larger. All of the patients without malignant exophthalmos showed a decrease in the eye manifestations. In two of the three cases with malignant exophthalmos there were no significant changes in the eyes, whereas in the other one the ophthalmopathy became worse.

The changes in the basal metabolic rate were similar to those observed following the use of thiouracil in the treatment of 152 patients (7) (Fig. 2). Five weeks were required for the average basal rate to become normal. In four of the eight patients in whom changes in the concentration of blood cholesterol were followed there was a significant elevation and in two subjects it rose above normal.

In one patient it is significant to compare the effect of treatment on the clinical manifestations of the disease with the results of certain laboratory tests. Preceding treatment the basal metabolic rate (B.M.R.) was plus 43 per cent and the protein bound iodine (P.B.I.) was 14 micrograms (normal 4–8) per 100 cc. of plasma. After treatment with tetramethylthiourea for 17 days the B.M.R. was plus 14 and the P.B.I. was 5 μg.; after 30 days the B.M.R. was plus 22 per cent and the P.B.I. was 7 μg.; after 53 days the B.M.R. was minus 2 per cent and the P.B.I. was 6 μg. The P.B.I. became normal before the patient became free of clinical manifestations of thyrotoxicosis and before the B.M.R. became normal. Later the patient developed a myxedematous appearance with puffy eyelids, drowsiness, slowed reactions, coarse voice and sensitivity to cold. At this time her B.M.R. was plus 2 per cent and her P.B.I. was 6 micrograms per 100 cc. of plasma. However, the cholesterol, which had been 149 mg. per 100 cc. of blood before treatment, had risen to 344. The myxedematous symptoms subsided with a reduction in the dose of tetramethylthiourea from 0.3 gm. daily to 0.2 gm., but no appreciable change in the basal metabolic rate resulted.

The 13 patients subjected to thyroidectomy had relatively little reaction during or following the operation, but as with thiouracil therapy, in some cases there was a large amount of bleeding from the thyroid gland.

4. *Toxic Reactions.* None of the patients experienced definite suppression of the granulocytes. In one patient the white blood count was 3200. Unfortunately this was not checked until the following day, when it was found to be 7700, in spite of continuing the drug in doses of 0.6 gm. daily. One patient developed urticaria, but after discontinuing the drug for five days the rash disappeared and did not reappear in spite of the fact that tetramethylthiourea was subsequently taken for two months in doses of 0.4 gm. daily. One patient developed a febrile reaction, but several days later full doses (0.6 gm. daily) of the drug were given with no reaction. Of the seven patients previously treated with thiouracil, three had had febrile reactions, making it necessary to discontinue treatment. Two of these three patients also had had a rash. Each of the three patients experienced a reaction within a few days after starting tetramethylthiourea; one of them developed a rash and fever, one fever and one a rash. These reactions subsided with cessation of therapy and recurred with a reinstitution of treatment.

No other toxic reactions were observed. The patients did not complain of the taste or smell of the medicine and did not have any gastro-intestinal disturbances.

DIETHYLTHIOUREA

Diethylthiourea (with symmetrically placed ethyl radicals) is a white, crystalline powder with a bitter taste and a slight odor. It is soluble at 37° C. to the extent of one gram in 1300 cc. of water. A standard solution kept in the icebox at 5° C. showed no change in concentration in one week. With Grote's reagent it develops a color which can be measured quantitatively by the methods previously described for thiouracil (6). As shown by a Hardy recording spectrophotometer the color produces a maximal absorption of light in the range between 590 and 620 mμ. In the estimation of diethylthiourea a 620 mμ light filter and a No. 6 diaphragm were used. The same recovery experiments were performed with diethylthiourea as with tetramethylthiourea. The average recovery from blood

was 96 per cent; from tissue, 97 per cent; and from urine 100 per cent.

Our observations indicate, as did Astwood's (1), that diethylthiourea is not quite as goitrogenic as thiouracil. This is true in spite of the fact that in rats and in humans a slightly higher blood level was obtained with diethylthiourea than with equal doses of thiouracil.

Four thyrotoxic patients were treated with diethylthiourea. None of these patients had previously had any treatment. The pre-treatment basal metabolic rate in one patient was plus 34 per cent. Therapy with diethylthiourea, 0.2 gm. three times daily, was instituted. However, in the subsequent 24 hours the patient complained of headache, anxiety, palpitation and slight dyspnea. With reduction in the dosage to 0.2 gm. twice daily these symptoms disappeared. Nine days after beginning treatment the basal metabolic rate was plus 43 per cent. At this time the dosage was increased to 0.2 gm. three times daily. The above mentioned symptoms returned, but they were not as prominent. Eight days after this increased dosage the basal rate was plus 45 per cent. In view of the persistence of the above complaints the dosage was reduced to 0.2 gm. twice daily. The untoward symptoms again disappeared, but the thyrotoxic manifestations remained unabated, the basal metabolism being plus 66 per cent one month after beginning therapy. At this point thiouracil was substituted and the basal metabolic rate became normal within three weeks.

Another patient, with a basal metabolic rate of plus 51, was given 0.2 gm. of diethylthiourea twice daily. Nine days later the basal rate had decreased to plus 38 per cent. The dosage was then increased to 0.2 gm. three times daily, but during the next six days the patient complained of increased nervousness, anxiety, headache, and tachycardia. Therefore, the dose was decreased to the original level. During the next 23 days there were four basal tests ranging from plus 23 per cent to plus 38 per cent. Although the patient experienced some improvement in her thyrotoxicosis the progress seemed too slow since the basal metabolic rate decreased only from plus 51 per cent to plus 33 per cent after treatment for six weeks. Thiouracil was substituted and the basal rate dropped to plus 4 per cent within 12 days.

A third patient, with a basal metabolic rate of plus 40 per cent, was given 0.2 gm. of diethylthiourea three times daily. This dose, which bothered the two previous patients, did not cause any disturbance in this patient. After two weeks the basal rate was plus 25 per cent, after four weeks it was plus 22 per cent, and after six weeks it was plus 20 per cent. The clinical changes were in accord with the changes in basal rate. After about four weeks of treatment with diethylthiourea the patient developed an urticaria, but this disappeared in spite of continuation of therapy.

A fourth patient, with a basal metabolic rate of plus 29 per cent, was given 0.2 gm. of diethylthiourea three times daily. Throughout the next ten days she was bothered with headaches, anorexia, nausea and, finally, vomiting. During this time her thyrotoxic manifestations became worse and her basal rate increased to plus 50 per cent. Consequently the diethylthiourea was discontinued and then treatment with tetramethylthiourea was begun, using the same dose. No untoward reactions occurred and the thyrotoxicosis rapidly subsided. The basal metabolic rate became normal within three weeks.

In each of these four patients there were frequent urinalyses, erythrocyte and leucocyte counts, estimations of the plasma chloride, carbon dioxide combining power of the blood, non-protein nitrogen, and a few estimations of the total serum proteins, but no significant changes were observed.

SUMMARY

Tetramethylthiourea has been used in the treatment of 30 patients with thyrotoxicosis. The changes in the clinical condition of the patient and in the basal metabolic rates were similar to those of 152 patients treated with thiouracil. No significant effects on the white count were observed. Three of the patients who developed febrile or skin reactions to thiouracil developed similar reactions to tetramethylthiourea. One of the nonthioura-

cil patients developed an urticarial reaction; tetramethylthiourea was discontinued for five days and then resumed without further trouble. Another patient developed a febrile reaction, but subsequently treatment was given with no reaction.

When tetramethylthiourea and thiouracil were given in doses of equal size to rats there was a higher concentration of the former in the blood and in the thyroid tissue. In man, treatment with tetramethylthiourea yielded a higher blood level and a smaller quantity of the drug in the urine than was true when thiouracil was given in equal doses.

Diethylthiourea was given to four patients with thyrotoxicosis, but these patients experienced a less satisfactory response than similar ones treated with tetramethylthiourea or with thiouracil. Doses of diethylthiourea which were as great as 0.6 gm. daily caused three of the patients to have unpleasant reactions. One patient reacted with urticaria, but this caused only temporary cessation of therapy.

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Antithyroid Drugs: II. Paraxanthine[1]

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THE EFFECTIVENESS of most of the antithyroid drugs that have been used in the control of thyrotoxicosis has depended upon their ability to interfere with the production of the thyroid hormone. However, the recent observations of Carter and his collaborators (1) suggested that possibly a drug had been found which would antagonize the effects of preformed thyroxin. These investigators found a substance, identified as paraxanthine (1:7 dimethylxanthine), in liver of the ox and the whale and in human urine, which in certain concentrations completely antagonized the action of thyroxin in converting a winter frog heart into a summer frog heart; it also abolished the calorigenic effects of thyroxin in rats. The maximal effects of paraxanthine were obtained when in each liter of solute 0.22 μg. of this substance was used for 1 mg. of thyroxin. The greater the deviation in the ratio of these two substances the less antagonistic was the effect.

The possible effectiveness of such a substance in thyrotoxicosis prompted us to investigate it further. Consequently, studies were made of the possible antagonism of paraxanthine to (a) the metamorphic effect of thyroxin in tadpoles, (b) the acceleration of oxygen consumption of liver slices produced by thyroglobulin, and (c) the excess thyroid hormone in thyrotoxicosis. Because these studies did not reveal an antagonistic action of paraxanthine the results are presented only briefly.

EFFECT ON THE NORMAL AND THE THYROXIN-ACCELERATED METAMORPHOSIS OF TADPOLES

Bullfrog tadpoles (*Rana Catesbiana*), were separated into eight groups with four animals in each group. Although the weights varied from 3 to 14 m., each group was sorted to have individuals with comparable weights. Each group was kept in a glass jar, containing one liter of tap water. The water was changed daily for the first week and subsequently every two days. The room was cool. The diet consisted of boiled spinach. Stock solutions of thyroxin and paraxanthine were prepared at weekly intervals, and were kept in the dark at 5° C.

The eight groups were treated as follows, the chemical being added to the water, except as noted: (1) no treatment, (2) 0.4 mg. of thyroxin, (3) 0.088 μg. of paraxanthine,[2] (4) 0.4 mg. of thyroxin and 0.088 μg. of paraxanthine, (5) 0.4 mg. of thyroxin, 0.088 μg. of paraxanthine and the same quantity of the latter was injected intramuscularly daily, (6) 0.4 mg. of thyroxin and 0.88 μg. of paraxanthine, (7) 1 mg. of thyroxin, and (8) 1 mg. of thyroxin, 0.088 μg. of paraxanthine and 0.088 μg. of paraxanthine injected subcutaneously three times daily. These doses were selected on the basis of the observation (1) that 0.22 mg.

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[2] We are indebted to Dr. R. O. Roblin of the American Cyanamide Company, Stamford, Connecticut, for the supply of paraxanthine.

of paraxanthine would completely antagonize the effect of 1 mg. of thyroxine. In some groups, however, the ratio was varied since there was a possibility that the quantitative effects of the drugs were different in tadpoles from the previous test-objects (1). Paraxanthine was given by injection as well as orally to some animals to insure its getting into the body.

At intervals of 3 days the animals were observed for changes in weight, total length, length of tail and of hind leg; after 28 days autopsies were performed, at which time the length of the intestines and the structure of the mouth were noted.

Paraxanthine neither inhibited nor augmented the maturation of the tadpoles. Thyroxin produced the effects which were expected; *viz.*, reduction in weight, decrease in total length and tail's length, rapid growth of hind legs, increased rate of development of the forelimbs, shortening of the intestines and maturation of the mouth. Paraxanthine when given with thyroxin in varying concentrations and by various routes caused no inhibition or acceleration of thyroxin's effects.

THE OXYGEN CONSUMPTION OF SURVIVING LIVER SLICES

The effects of paraxanthine on the hypermetabolic action of thyroglobulin was studied with the Warburg technique. Each Warburg flask contained 2.7 cc. of a phosphate salt medium. To this was added 0.3 cc. of a solution of the test-substances. Thin slices of liver of a guinea pig were added. The mixture was shaken for one hour at 38° C. Eight experiments were conducted, using in each three control flasks, two with thyroglobulin and two with thyroglobulin and paraxanthine. The same amount of thyroglobulin was added in each experiment. The quantity used was calculated as being *ca.* 2.75 mg. of thyroxin. In five experiments 0.605 μg. of paraxanthine was used. The relative amounts of these substances used were chosen on the basis of the optimum ratios observed by Carter, *et al.* (1). In two experiments, ten times this concentration of paraxanthine was used, and in one experiment only one-tenth the usual amount was used. However, the variations in the concentrations of paraxanthine caused no essential change in the results. The average consumption of oxygen in the flasks containing thyroglobulin was 4.9 cubic millimeters per hour for each milligram of dry liver; the average for the flasks with paraxanthine and thyroglobulin was 4.5, and for the vessels without either substance the average was 3.0. Therefore, the thyroglobulin caused a distinct increase in the rate oxygen was consumed by the slices of liver, and paraxanthine did not exert a significant effect in inhibiting this reaction.

EFFECT OF PARAXANTHINE ON A PATIENT WITH THYROTOXICOSIS

Paraxanthine was administered for 11 consecutive days in various dosages and by different routes to a female patient, aged 35, with typical Graves' disease, which had its onset six months previously. Effects of the paraxanthine on the clinical characteristics of the disease and on the basal metabolic rate (B.M.R.) were recorded. Estimations of the basal metabolic rate were performed daily, except Sundays. Before any treatment the values were plus 43, plus 38, plus 28 and plus 35 per cent. Paraxanthine was given in doses of 3 mg. daily for two days; the substance was put in the patient's drinking water, and the patient drank some of it at least every hour from 5 a.m. until 9 p.m. The metabolic rate following this therapy was plus 40 per cent. A few minutes after this test, 0.5 mg. of paraxanthine in 2 cc. of saline was injected subcutaneously, and this was repeated in 30 minutes; after another 30 minutes the metabolic rate was plus 38 per cent. Throughout the remainder of the day the patient drank 2 mg. of the drug in her drinking water, but on the following morning the metabolic rate was plus 46 per cent.

Paraxanthine in doses of 1 mg. was then given in the water for two days. The metabolic rates following this treatment were plus 40 per cent and plus 44 per cent, in spite of the fact that some of the solution was drunk during a three hour interval preceding the latter test. During the next 24 hours 6 mg. was similarly ingested, but at the end of this period

the metabolic rate was plus 46 per cent. During the subsequent 24 hours 1.5 mg. in 6 cc. of saline was given subcutaneously, every six hours. At the end of this period the metabolic rate was plus 20 per cent. Then 6 mg. in sterile mineral oil was given intramuscularly, daily for two days, but after this the metabolic rate was plus 43 per cent. At this time 1 mg. of paraxanthine in 1000 cc. of normal saline was given intravenously, and on the following day, preceding the metabolism test, 3 mg. of the drug in 1500 cc. of saline were given intravenously during a period of three hours. When the metabolic rate was determined 30 minutes after cessation of the infusion it was found to be plus 39 per cent. There was no subsequent treatment and on the following morning the metabolic rate was plus 40 per cent. Throughout the entire 11 days of treatment with paraxanthine there was no significant change in the clinical condition of the patient nor in the metabolic rates.

SUMMARY

Observations to determine whether paraxanthine exerts an antagonistic effect against thyroid hormone were made in the following circumstances: 1) the metamorphosis induced in tadpoles by thyroxin; 2) the calorigenic action induced in surviving liver slices by thyroglobulin; and 3) a patient suffering from thyrotoxicosis. Paraxanthine was found to be ineffective in these experiments.

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The Excretion of 17-Ketosteroids by Diabetics

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DIABETES is complicated occasionally by impotence in men and by retardation of physical and sexual development in children of adolescent age. Since impotence may be associated with a decrease of testicular function, a study of the excretion of 17-ketosteroids by diabetic men seemed indicated, inasmuch as it furnishes some indication of testicular function. Interpretation of results, however, is complicated by the contribution of the adrenal glands to the total excretion of 17-ketosteroids. Therefore, diabetic women were also included in the study, since in women the adrenal glands furnish almost, if not entirely, all of the urinary 17-ketosteroids (2, 7). At puberty, associated with the sexual development and growth, there is normally a rapid rise in the excretion of the 17-ketosteroids derived from the testes and from the adrenal glands (12). Therefore, the excretion of these substances by diabetic children of adolescent age was studied in relation to sexual and physical development.

Very little is known about the excretion of 17-ketosteroids by diabetic patients. Fraser, Forbes, Albright, Sulkowitch and Reifenstein (6) have determined the excretion of 17-ketosteroids by six diabetic patients who were between 41 and 67 years of age. The values obtained were somewhat below normal, but they were thought to be compatible with the poor condition of the patients and the advanced age of three of them.

Pathologic changes in the testes of diabetic patients have been described by Koch (8) who regarded them as circulatory in origin and the result of arteriosclerosis. Atrophy of the seminiferous tubules and, in some instances, an increase of interstitial tissue were found. Kyrle (9) also described the occurrence of testicular atrophy. Warren (14), who concluded that sterility of diabetic men was secondary to malnutrition, frequent toxemia, and attacks of acidosis, observed cessation of spermatogenesis and thickening of the basement membrane of the seminiferous tubules when the disease was untreated or poorly treated. Alterations of the normal picture were not observed in cases in which the patients were treated adequately.

According to White and her associates (13, 15, 16, 17), diabetic dwarfism is primarily the result of failure of the pituitary body. In support of this view these authors pointed out the similarity of the physical characteristics of diabetic and hypopituitary dwarfs, and the favorable results that are said to follow adequate therapy with thyroid substance and extract of the anterior lobe of the pituitary body. According to another view,[2] this condition is the result of quantitative undernu-

[1] Abridgment of thesis submitted by one of us (S.M.) to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

After this paper was written Dr. Miller entered the armed forces, and is now Lieutenant, Medical Corps, Army of the United States.

[2] This view is held by our colleagues, Drs. Kepler, Rynearson, Sprague and Keating, who are on the diabetic service at the Mayo Clinic.

trition, particularly with respect to protein. It could not be expected that a quantitative estimation of the 17-ketosteroids excreted by the retarded children would yield evidence in support of either of these views. A low excretion of these substances probably would be expected from either cause. It was thought, however, that a survey of diabetic children might give information of value.

METHODS

The patients who were selected for study were in good physical condition aside from their disease. Patients who had associated conditions such as active ulceration or infection were not included. The collection of urine was made at or near the end of the period of establishment of the best possible control of the diabetes by diet and insulin.

All patients less than 21 years of age were regarded as juvenile diabetics. In order to have standards for evaluation of the results obtained with this group, it was considered essential to establish normal values by our method of procedure. Accordingly, the excretion of 17-ketosteroids by 99 school children between 12 and 18 years of age was determined

The specimens of urine were collected during a 24 hour period, with 15 cc. of 6 *N* hydrochloric acid as a preservative. The patients and the normal children were carefully instructed in the method of collection and impressed with the necessity for completeness. At the conclusion of the 24 hour period, they were questioned, and if there was any doubt about the completeness of collection the specimen was discarded. It was possible to make only one determination for each subject in most instances.

The urine was boiled ten minutes with 0.1 volume of concentrated hydrochloric acid, and then extracted for one hour in a continuous extractor with carbon tetrachloride. The carbon tetrachloride was washed according to the method of Talbot and his co-workers (11), and then was distilled under reduced pressure. The residue was dissolved in an appropriate amount of absolute alcohol, and the amount of 17-ketosteroids was determined by the technic of Callow, Callow and Emmens (3). The values were corrected by the equation suggested by Talbot, Berman and MacLachlan (10) and used by Engstrom and Mason (5).

RESULTS

The results obtained for adult diabetic patients are plotted in Figure 1. Although many values lie within the normal range (for men, 10 to 21 mg.; for women, 6 to 17 mg. in 24 hours), 56 (88 per cent) of the 64 values lie below the average normal values while 27 values (42 per cent) fall below the minimal normal levels. There is obviously a definite trend toward a lowered excretion of 17-ketosteroids by adult diabetic patients. This trend is even more marked in the case of the men. Of 38 men, 20, or 52 per cent, excreted less than the minimal normal amount. Some of these values are not significantly lower than our lowest normal value, but the trend is unmistakable. This downward trend, which is evident in both sexes, suggests that testicular function and also some phase of adrenal cortical function are impaired by the diabetes in so far as these functions are reflected by the amount of 17-ketosteroids excreted in the urine.

Examination of Figure 1 also reveals that the excretion of 17-ketosteroids by five of seven men with decreased libido or potentia was significantly below the normal level. This situation suggests that their impotence may have been the result of impaired testicular function. It is to be regretted that a therapeutic test of this conclusion could not be made. However, there were nine other men who excreted comparable amounts but who did not complain of impotence. One can only speculate as to the exact cause of the decreased function of the testes. Two of the men with impotence excreted amounts of 17-ketosteroids which were within the normal range; in one instance, the excretion was at the upper limit of normal. It is not likely that their impotence could be attributed to failure of testicular function.

In view of the generally depressed excretion of 17-ketosteroids by diabetic patients,

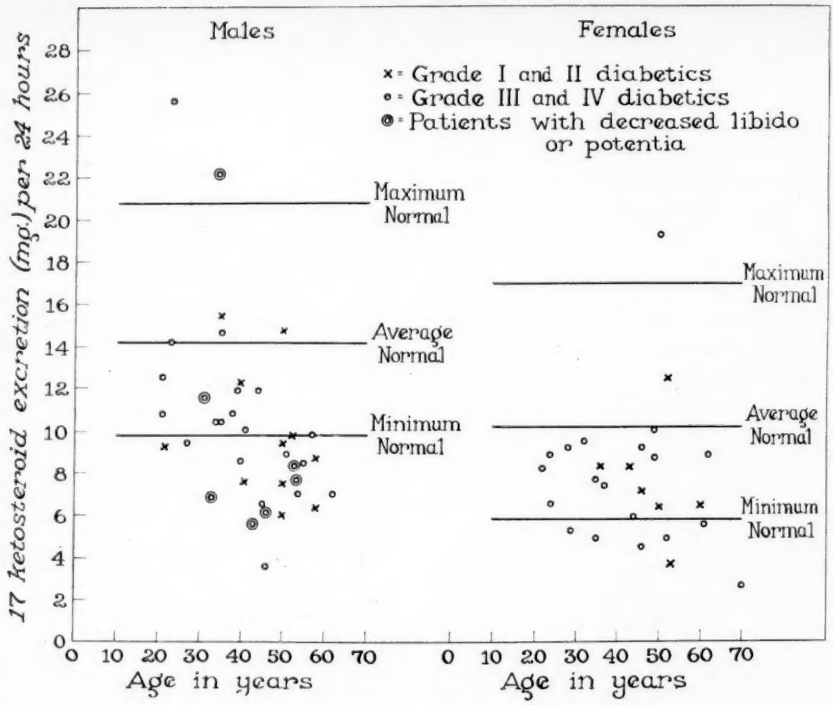

FIG. 1. Excretion of 17-ketosteroids by adult diabetic patients.

it is surprising to find that two patients were excreting more than our maximal normal amount. The thought arises that perhaps in these two cases hyperplasia of the adrenal glands was associated with the diabetes, but in the absence of other evidence, the significance of this result remains obscure.

The results are arranged in Table 1 in groups according to age and according to the severity of the disease. Grades 1 and 2 include diabetes that can be controlled by dietary means alone; grades 3 and 4 include diabetes that requires insulin in addition to dietary measures. Consideration of the average values reveals that there is no obvious relation between the excretion of 17-ketosteroids and the age of the patients or the severity of the disease. The first two figures in column 12 might be considered at first glance to indicate a greater excretion by younger individuals,

TABLE 1. URINARY EXCRETION OF 17-KETOSTEROIDS BY ADULT DIABETIC PATIENTS

Age, years	Diabetes, grade 1 or 2						Diabetes, grade 3 or 4					
	Excretion of 17-ketosteroids; mg. in 24 hours						Excretion of 17-ketosteroids; mg. in 24 hours					
	Males			Females			Males			Females		
	No.	Range	Av.	No.	Range	Av.	No.	Range	Av.	No.	Range	Av.
20 to 29	1	9.3	9.3				5	9.4 to 25.6	14.5	5	5.3 to 9.2	7.6
30 to 39	1	5.4	5.4	1	8.4	8.4	8	6.9 to 22.1	12.3	4	4.9 to 9.5	7.4
40 to 49	2	7.6 to 12.3	9.9	2	7.8 to 8.3	7.7	7	3.6 to 11.9	7.4	5	4.5 to 10	7.7
50 to 55	6	6 to 14.8	10	2	3.8 to 6.4	5.1	5	7 to 8.9	8.1	2	4.9 to 19.3	12.1
56 to 65	2	6.4 to 8.7	7.5	1	6.5	6.5	2	7 to 9.8	8.4	2	5.6 to 8.9	7.2
65 to 70										1	2.7	2.7

TABLE 2. URINARY EXCRETION OF 17-KETOSTEROIDS BY NORMAL BOYS AND GIRLS

Age, years	Boys					Girls					Average excretion of 17-ketosteroids by both boys and girls, mg.
	No.	Height, cm.	Weight, kg.	Excretion of 17-ketosteroids; mg. in 24 hours		No.	Height, cm.	Weight, kg.	Excretion of 17-ketosteroids; mg. in 24 hours		
				Range	Av.				Range	Av.	
12	9	140–163	38.0–52.2	1.0– 2.3	1.8	7	143–162	30.4–52.7	1.6– 5.3	2.9	2.3
13	6	150–187	33.0–72.8	0.9– 8.0	3.4	9	154–166	37.0–52.7	1.0– 5.6	3.0	3.2
14	11	143–184	48.4–84.2	3.3–15.6	6.3	9	152–169	46.8–64.5	3.6–10.0	6.0	6.1
15	9	165–180	54.1–70.5	4.1–11.3	6.9	7	152–169	48.2–62.7	3.5– 9.9	5.5	6.2
16	8	168–180	60.5–74.5	3.4–10.5	7.6	10	155–169	46.5–56.2	3.8–13.1	7.5	7.5
17	7	165–180	58.7–79.6	3.7–12.7	8.5	6	156–169	49.1–61.8	3.3– 9.8	6.6	7.5
18	1	180	72.7	6.0							

but these averages are distorted by the two very high values which were just mentioned. It is quite probable, however, that the very low value for the woman 70 years of age is more the result of advanced age than of the diabetes.

The results obtained for the normal school children are summarized in Table 2 and charted in Figure 2. The values obtained for the various age groups are very similar to those obtained by Talbot and his co-workers (12).

There were seventeen diabetic patients less than 21 years old available for study; 14 were 12 years of age or older. Of the 14 patients who were more than 12 years of age, five were retarded in physical and sexual development and four of these were boys. The results are charted in Figure 3 in comparison with the normal values. It will be noted that all four of the boys who were underdeveloped were excreting amounts of 17-ketosteroids which were well below the minimal amounts for normal children of the same ages. The one girl excreted an amount which was well within the normal range. She was just 12 years old and had not yet shown signs of puberty.

The results obtained for the three retarded boys aged from 18 to 19 years show very clearly a deficiency of testicular function in agreement with the lack of development of the sexual structures. The very low values also indicate a deficiency in that function of the adrenal cortex which becomes manifest at puberty by an increased excretion of 17-

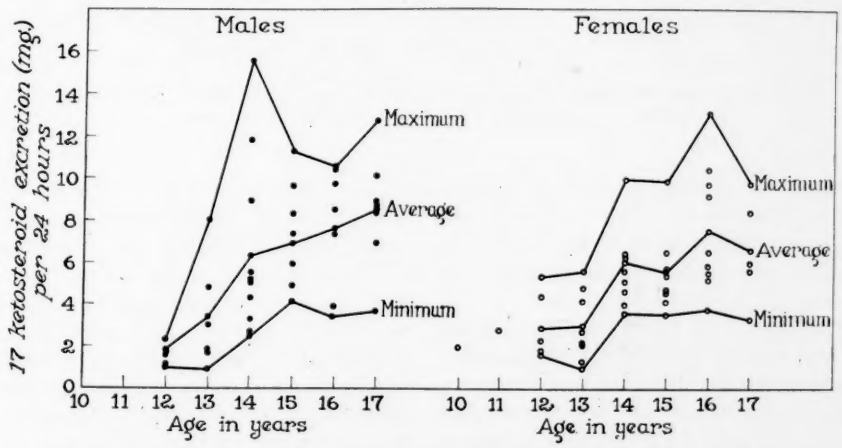

FIG. 2. Excretion of 17-ketosteroids by normal male and female individuals between twelve and seventeen years of age.

ketosteroids. Studies of castrate men (16) and of men with Addison's disease (4, 6) indicated that the adrenal cortices normally are the source of the major part of the urinary 17-ketosteroids.

COMMENT

The results obtained in this study reveal a distinct lowering of the excretion of 17-ketosteroids by diabetic patients of all ages and with all degrees of severity of the disease. One can only speculate as to the relation of the decreased excretion to the disease. Suggestions as to possible relations are not warranted in view of the many possible variables which were largely uncontrolled in this study. It does seem justifiable to conclude, however, that diabetes often has an effect on the testes and adrenal glands which results in a lowered excretion of 17-ketosteroids and which is not related to the degree of impairment of carbohydrate metabolism.

SUMMARY

This report is based on a study of the excretion of 17-ketosteroids by 64 adult and 17 juvenile diabetic patients and by 99 normal school children. The results indicate that diabetic patients of all ages generally excrete a smaller amount of 17-ketosteroids than do normal persons. There was no correlation between the lowering of the amount of 17-ketosteroids excreted and the severity of the diabetes. Five of seven men with impotence excreted less than the minimal normal amounts, but nine men who did not complain of impotence excreted comparable amounts. Juvenile patients who were retarded in physical and sexual development excreted amounts of 17-ketosteroids which were much less than

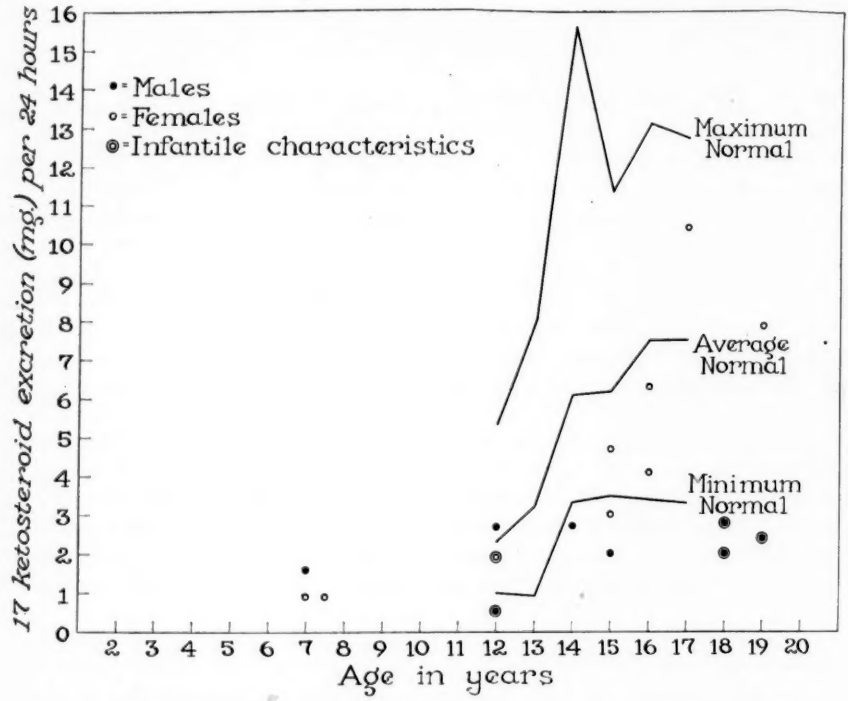

FIG. 3. Excretion of 17-ketosteroids by juvenile diabetics compared with that by normal male and female individuals between twelve and seventeen years of age.

the amounts excreted by normal children of the same age, but comparable to the amounts excreted by normal children of early adolescent age. It is concluded that diabetes often has an effect on the testes and adrenal cortex which is reflected by a lowered excretion of 17-ketosteroids but which is not related to the degree of impairment of carbohydrate metabolism.

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Chronic Hemospermia; Its Origin and Treatment with Estrogen[1]

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THE PROBLEM of the origin of the blood in chronic hemospermia was attacked by a chemical study of the ejaculate collected in serial fractions, the three glass test, and it was found that the hemorrhage arises from the vesicular apparatus. On theoretical grounds it was appropriate to test the effect of estrogen as a therapeutic agent. Six patients were treated, and in five the hemorrhage ceased.

Blood in the semen is caused by many agents. It is useful to differentiate between hemospermia of brief duration and the more chronic condition. Acute hemospermia is observed not infrequently and the causes are often obvious; as a few common examples we cite acute prostatitis, ejaculation before complete healing following prostatic resection, and ejaculation following trauma. These episodes of bleeding are temporary in the majority of cases and will not be considered further in this paper. Of entirely different etiology and course is chronic hemospermia.

Patients with chronic hemospermia are not infrequently seen in urological clinics. The condition is characterized by its chronicity and its resistance to various methods of treatment. Aside from the bloody semen, usually little is found on general or urological examinations. The condition has been observed to persist uniformly over months and years without regression, but with little damage to general health, although it is sometimes a source of considerable anxiety to the patient.

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REVIEW OF THE LITERATURE

Observations on the nature of hemospermia have been recorded at infrequent intervals. Lydston (13) in 1894 reported five cases of hemospermia, and in his experience the disease was associated variously with congestion behind a stricture, seminal vesiculitis and "unbridled license, short of physical indulgence." The theory (16) of "hemorrhage ex vacuo," which states that after a period of prolonged continence, the over-distended vesicle is suddenly decompressed and a hemorrhage occurs has been advanced. Shropshire (22) distinguished between vesicular hemorrhage, in which the semen is uniformly pink, and prostatic bleeding in which the semen is streaked with blood and small clots. Ashkar and Issa (1) reported seven cases of bilharzial seminal vesiculitis associated with hemospermia. In a recent review Parker (19) reported five cases of hemospermia in which the etiological agents were respectively testicular trauma, cyst and papilloma of the verumontanum, spermatocele and tuberculous seminal vesiculitis. He considers gross masturbation or sexual excess as the most frequent cause for hemospermia and tuberculous seminal vesiculitis as the second most important cause. Obviously the chief interest of these articles is historic. Considering the frequency of sexual excesses, both in partnership and alone, and the relative rarity of chronic hemospermia, it will be realized

that frequent sexual exercise is not apt to rupture blood vessels.

Herbst and Merricks (9) reported that hemospermia may occur with no demonstrable cause and that "a huge vesicle filled with blood may respond well to empirical treatment with nitrate of silver instillations."

CLINICAL OBSERVATIONS

During the past seven years, twenty patients with the complaint of blood in the semen were examined in the Urological Division of the University of Chicago Clinics (Table 1). In eight of these cases the duration of symptoms was one year or longer. Of six cases in which there was a spontaneous complete disappearance, the duration of symptoms was one month or less in five patients. Factors associated with hemospermia were trauma (hemorrhoidectomy) in one, prostatic hypertrophy in one, recurrent epididymitis in one, chronic prostatitis in five, renal calculi in one, hypertension in three, epilepsy in one and Pick's disease in one case. In eight cases no contributing factor was demonstrated. The age of the patients ranged from twenty to seventy-one years with a distribution favoring the third and sixth decades. Each patient was questioned as to the frequency of intercourse and the character of the ejaculate. In none of the twenty cases was ejaculation so frequent as to constitute sexual abuse, and in no case was there a history of a bloody ejaculate occurring as the result of intercourse after a period of prolonged abstinence. Of interest is the history of a man, a widower, for ten years, who every three to four weeks had spontaneous nocturnal seminal emissions which suddenly became bloody one year ago and remained bloody ever since. Of the associated factors listed above, few had any etiological implications, since in a heterogeneous group of men of this age one might find such a distribution of these factors. The case in which a hemorrhoidectomy preceded by one week the onset of hemospermia may logically be explained by trauma to the secondary sex organs, since there was abrupt and complete disappearance of the hemospermia spontaneously. When questioned as to the character of the ejaculate some of the patients stated that the first portion of the semen was white or only faintly colored whereas the succeeding portions were more highly colored. Of seven cases only two described the semen as bright red in color; the remaining five termed it brown or red-brown. In no case was genitourinary tuberculosis discovered, and case re-

TABLE 1

Patient	Age	Duration of hemospermia	Associated disease	Comment
M.J.	20	3 da.	Epilepsy	Spontaneous remission, 2 wk.
S.P.	20	2 yr.	Prostatitis	Spontaneous improvement, 1 mo.
Z.H.	21	2 wk.	None	Spontaneous remission, 1 wk.
G.M.	24	1 wk.	Hemorrhoidectomy	Spontaneous remission, 1 mo.
S.S.	28	5 mo.	Recurrent epididymitis	Treated with estrogens
F.H.	29	1.5 yr.	Prostatitis	No improvement, 1 mo.
M.L.	35	1 mo.	None	Spontaneous remission, 1 wk.
H.P.	36	1 mo.	None	Treated with estrogens
Y.R.	36	4 yr.	None	Treated with estrogens
S.F.	40	1.5 yr.	Hypertension	Spontaneous remission, 1 mo.
M.M.	41	4 yr.	Prostatitis	Treated with estrogens
M.T.	47	1 wk.	None	Not followed
L.H.	51	10 mo.	Hypertension	Not followed
A.C.	51	1 mo.	Prostatitis, Pick's disease	Spontaneous remission, 9 mo.
I.E.	53	1.5 yr.	Hypertension	Not followed
P.F.	54	1.5 yr.	Passed stones 9 mo. ago	Treated with estrogens
W.J.	55	1 yr.	None	Treated with estrogens
K.F.	59	1 yr.	None	Treated with estrogens
H.F.	60	5 wk.	Prostatic Hypertrophy	Not followed
R.H.	71	5 yr.	None	Not followed

ports of patients with known genito-urinary tuberculosis revealed not one instance of hemospermia.

In the past year, nine patients with hemospermia have been observed; two had symptoms of less than two weeks duration which disappeared spontaneously. In the remaining seven cases, the semen had been consistently bloody for one year or longer in five cases, and one month and five months, respectively, in the other two cases. The urologic examination in these cases was negative, with the exception of one case of chronic prostatitis in which two years of treatment with prostatic massage and baths failed to cause remission of the hemospermia. These seven cases were selected for study because they were of unknown etiology and because they presented a history of successive bloody ejaculations over long periods of time.

We consider the term chronic hypospermia to apply when blood persists in the semen for more than one month; this differentiates it from acute hemospermia which might have disappeared spontaneously.

MATERIALS AND METHODS

With one exception semen specimens were obtained by direct ejaculation into a glass container. Fractionated collections of the semen were made in 3 glasses as ejaculated; when the volume was small the semen was collected in a single tube. Within 15 minutes samples were withdrawn for determination of reducing substances by the Shaffer-Hartman-Somogyi (20) blood sugar method. Where volumes permitted the fibrinolysin value (11) was determined on each glass by measuring the time required for 0.1 ml. of semen to liquefy the clot produced by action of 0.5 mg. of thrombin on 30 mg. of fibrinogen,[2] at pH 6.7 and at 37°C. The acid phosphatase value was determined by a slight modification of the method of King and Armstrong, using acetate buffer at pH 5 and the results are expressed in the units of these authors (12). Microscopic examination of the semen in each glass was done to determine motility and morphology of the sperm, and erythrocyte and spermatozoa (23) counts were made in a counting chamber. In order to determine whether erythrocytes were a normal component of the semen, smears of ten normal semen specimens obtained by manual ejaculation were stained with Wright's stain.

RESULTS

Gross examination of the fractionated ejaculate collected in three glasses showed little or no blood in the first glass and progressively greater amounts of blood in the second and third glasses. In two cases the semen was bright red and in the others the color was rusty brown.

The concentration of glucose—a component arising from the seminal vesicle (10)—was found to be greatest in the third glass, whereas the prostatic moieties, fibrinolysin and acid phosphatase were greatest in the first glass.

In normal semen erythrocytes were not found although leucocytes and epithelial cells were always observed in small numbers. Microscopic examination of the semen of patients with hemospermia always revealed a typical picture of erythrocytes, singly and in agglutinated clumps, and also large macrophages containing yellowish-brown, coarse granular inclusions; an unusual number of epithelial cells or leucocytes was not found. In the patient *Y.R.* there was a terminal hematuria which disappeared with the cessation of hemospermia. Cysto-urethroscopic examinations in these patients were uniformly negative.

On the basis of these observations it is certain that the hemorrhage in all of these cases of chronic hemospermia arose in the seminal vesicle.

THE TREATMENT OF HEMOSPERMIA

Estrogen, ethinyl estradiol,[3] was adminis-

[2] The authors are indebted to Dr. J. F. Biehn, Abbott Laboratories, North Chicago, Illinois, for donations of sterile thrombin, and to Dr. J. T. Edsall for supplying human fibrogen preparation *HF 132 B*. This product of human plasma fractionation was prepared from blood collected by the American Red Cross by the Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts, under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

[3] This compound was generously supplied under the trade mark, Estinyl, by Dr. Erwin Schwenk, Schering Corporation, Bloomfield, New Jersey.

tered orally to six patients with chronic hemospermia; the dosage of 0.05 mg. in all cases was varied from three times a week to twice daily depending on the response obtained; the treatment lasted from three to seven weeks except in the case of *M.M.*, in which the female sex hormone was evidently ineffective. Four patients had complete remissions at the time of writing (2, 2, 3, and 8 months). The results were unsatisfactory in two patients (Table 2). In one of these the duration of treatment (three weeks) was considered to be too brief, and in the other the patient was refractory to oral administration of estrogens. The evidence for the lack of effect of estrogen was the persistence of spermatozoa in the semen for six months. In one patient, *Y.R.*, there was a complete remission of hemospermia which lasted for three months, but after the cessation of estrogenic therapy, there was a recurrence of blood in the semen.

TABLE 2. RESULTS OF ESTROGEN THERAPY

Patient	Ethinyl estradiol 0.00005 gm.	Duration of treatment	Result of treatment	Duration of remission	Comment
H.P.	twice daily	3 wk.	clear	3 mo.	
M.M.	twice daily	6 mo.	clearer		Irregular therapy
P.F.	alternate days	6 wk.	clear	8 mo.	
S.S.	twice daily	2 mo.	clear	6 wk.	Acute epididymitis
W.J.	twice daily	4 wk.	clearer		3 mo. later, clear
Y.R.	thrice weekly	4 mo.	clear	9 wk.	retreated recurrence successfully after 8 weeks.

In two cases enlargement of the breast with areolar tenderness was noted. During estrogenic treatment the volume of the semen was greatly reduced; it liquefied more rapidly and, when free from blood, was white in color; the characteristic yellow pigment of the secretion of the seminal vesicle was not present. The glucose concentration in the semen in the case of *Y.R.* was reduced from 293 mg. to 70 mg. per 100 milliliters.

PROTOCOLS

Case 1. P.F., a salesman, aged 54 years, complained of no symptoms except blood in the ejaculate constantly present for nine months. The blood pressure was 136/78 mm. of mercury. Physical examination was not remarkable. The semen was dark brown in color, contained many motile spermatozoa and clumps of erythrocytes. Ethinyl estradiol, 0.025 mg. daily, was administered orally for 42 days. Blood completely disappeared from the ejaculate and the semen was normal eight months later, at which time the spermatozoa count was 150 million per cc.

Case 2. Y.R., a laborer, aged 36 years, was first examined on July 17, 1943 when he complained of blood in the semen of four years' duration; there was occasionally a burning urethral pain during coitus. He had been treated by various physicians, who massaged the prostate and painted the urethra with silver nitrate. The blood pressure was 130/80 mm. of mercury. Physical examination was normal except for a distended right seminal vesicle. The terminal portion of the urine was grossly bloody and the semen was bright red in color. Cystoscopy revealed no pathology.

No treatment was prescribed and the hemospermia continued unabated until April 19, 1944. Ethinyl estradiol, 0.05 mg. daily, was administered orally for 63 days with complete disappearance of seminal blood. Hemospermia recurred three months later. A second similar treatment was followed by a second relapse. At the present time the semen contains several "rice granules" of rusty blood.

Usually during therapy there were slight decreases in the prostatic functions, judging from the decrease of acid phosphatase and fibrinolytic activities. In two subjects the acid phosphatase was diminished to one third the original level, whereas in four cases there was a slight increase or no change. The fibrinolytic activity was decreased from 35 to 75% in four cases and increased 25 to 50% in two cases during treatment with estrogens (Table 3). In the majority of cases the

TABLE 3. SPERMATOZOA AND PROSTATIC ENZYMES BEFORE, DURING AND AFTER ESTROGEN TREATMENT

Patient	Ethinyl estradiol mg. per day	Days	Spermatozoa Millions per ml. Before	During	After	Fibrinolysin Time in hours Before	During	After	Acid phosphatase K. & A. units per ml. Before	During	After
V.R.	0.05	63	103	30	50	3.1	4.6	2.5	1150	510	1267
S.S.	0.10	42	1	1	10	2.7	1.3	1.3	859	1010	670
W.J.	0.10	35	150	50	—	3.0	3.9	—	68	480	—
H.P.	0.10	21	80	125	125	13.0	19.0	21.8	1205	1200	860
M.M.	0.10	91	65	2	—	1.1	9.2	—	908	176	—
P.F.	0.025	42	200	10	150	4.7	3.4	2.9	488	768	1390

spermatozoa count was decreased to one third of the pretreatment level after a total of about 3.0 mg. of ethinyl estradiol had been given. This total dose also increased the number of morphologically abnormal and nonmotile spermatozoa to about five times the original levels. Following cessation of treatment there was prompt recovery of spermatozoa to a normal number with a disappearance of the atypical forms.

DISCUSSION

It has been established by chemical study of the fractionated ejaculate that the prostate and the seminal vesicle do not empty simultaneously on ejaculation, but that prostatic excretion precedes the vesicular emptying in a roughly 1-2 relationship (Table 4). Segregation or predominance of blood in the last glass of the multiple-sample ejaculate demonstrates that in all of the present cases blood arose from the vesicular apparatus, seminal vesicle or ejaculatory ducts; one cannot distinguish between these areas by the present technique, but certainly the prostate is not the source of the bleeding.

TABLE 4. CHEMICAL COMPOSITION OF FRACTIONS OF THE EJACULATE.

Glucose arises chiefly from seminal vesicles; the other components are excreted chiefly or exclusively by the prostate.

Component	Fraction of ejaculate First	Last
Citrate, mg. % (23)	770	120
Calcium, mg. % (23)	52	20.4
Acid phosphatase units, 1 ml. (22)	2760	300
Glucose, mg. % (21)	157	377
Fibrinolysin, minutes per test	120	288

The prostate has a lower threshold to androgens than the seminal vesicles. Working with crude extracts of the testis, Moore and Gallagher (15) found that about three times as much androgen was required to produce effects on the seminal vesicle as on the prostate. This has been confirmed with pure androgens (5, 17). This explains why suppression of activity of the seminal vesicles occurred with retention of prostatic function and the ability to produce an ejaculate.

Estrogen injections in man produces a marked decrease in seminal volume (7). Estrogen administered to rodents causes an increase of weight of the seminal vesicle due to growth of smooth muscle in the castrate (3, 5 18) as well as in the normal adult (18). In intact male rats estrogen causes atrophy of the epithelium of the seminal vesicle with suppression of its secretions. Estrin in adequate dosage causes in the prostate a stratified squamous metaplasia which is completely reversible following cessation of estrin administration (4). These observations fall in with the data obtained in man in the present study; namely, relatively small doses of estrogen greatly depressed or eliminated the function of the seminal vesicles while prostatic secretion, which predominated in the ejaculate, persisted, hence providing a measurable ejaculate. The decreased volume of semen returned to normal on discontinuing the estrogen, with the important difference that often blood was absent.

For years it has been established that estrogen depresses or abolishes formation of sperm in the testis of laboratory animals; Heckel and Steinmetz (8) have observed that a like effect occurs in man. We have confirmed these observations, but in each patient spermatozoa of normal morphology reappeared in normal number some weeks after discontinuing treatment. It should be emphasized that the

estrogen dosage was small and the treatment brief; it is to be expected that prolonged administration of estrogen at high dosage will permanently damage the germinal epithelium.

While we have established that chronic hemospermia arises from the seminal vesicle, we acknowledge complete ignorance of the pathology underlying the condition. Blood in the semen is a symptom and not a disease. It was predictable that no single therapeutic agent would arrest all hemorrhage into the semen and this prediction has been confirmed. Chronic hemospermia, because of its vesicular origin, chronicity and benign prognostic significance, may tentatively be considered as a single entity. Estrogenic treatment causes cessation of bleeding in some patients; it is simple, and low dosage for brief periods does not cause permanent damage.

CONCLUSIONS

In cases of chronic hemospermia the blood was found to arise from the seminal vesicular apparatus. A low dosage of ethinyl estradiol caused complete cessation of hemorrhage in 5 of 6 cases; in 1 of these there was return of bleeding after 3 months. An appropriate dosage of estrogen causes a temporary suppression of function of the seminal vesicle with maintenance of prostatic function in man.

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CASE REPORT

COINCIDENTAL ADENOMAS OF ISLET-CELLS, PARATHYROID GLAND AND PITUITARY GLAND

We wish to describe the clinical syndrome and treatment of tumors of three endocrine glands, which occurred simultaneously in a young sailor. A careful search of the medical literature reveals no other case in which the association of pituitary, parathyroid and islet cell adenomas was recognized and treated during life. However, Lloyd (4) in 1929 reported tumors of these three glands found at autopsy in a patient who died from the effects of an enormous pituitary tumor, but no clinical studies for hyperinsulinism or for hyperparathyroidism were made, and these conditions were not suspected. The association of these three clinical syndromes in one patient probably represents an entirely new clinical entity.

The remarkable young man we observed developed typical hyperinsulinism during July, 1942, following an operation for left ureteral stone. An adenoma of the islands of Langerhans was removed in September, 1942, with complete cure of the hyperinsulinism. The ill omen, first revealed by the earlier appearance of renal stone, was not accounted for and in October, 1942, a large stone had to be removed from his right kidney. This was his third major operation within three months, and within another month recurring stones were found in both kidneys. The diagnosis of hyperparathyroidism was suggested, because of the discovery of excessive excretion of calcium in the urine and a high blood serum calcium. However, this finding was confused by the revelation that he had reliable radiographic evidence of a pituitary tumor for which he received a prolonged course of roentgen therapy. From time to time repeated calcium studies confirmed the impression that he also had hyperparathyroidism. Finally in March, 1944, a parathyroid adenoma was removed. The day after this operation, the urinary calcium excretion and the serum calcium became normal. Soon the renal stones began to decrease in size and he passed small stones. During the following three months he gained 15 pounds.

The presence of the pituitary tumor has not been confirmed by operation, but in addition to the radiographic evidence he has developed a temporal quadrant defect in his visual fields typical of pituitary tumor. This young man is truly a follower of Job, for he also has a large duodenal ulcer from which he has had several massive hemorrhages within the past two years.

The association of pituitary and parathyroid tumors has been reported before. Cushing and Davidoff (1) in 1926 found, in a group of autopsied acromegalics, marked proliferative activity in the parathyroids in one case and parathyroid adenomata in two cases. Houssay also has observed this (3). In his Harvey Lecture (3) in 1935, Houssay pointed out that hypophysectomy in dogs is followed by regressive lesions which can be seen in the parathyroids microscopically, but the blood calcium is not affected. He then found that if the pancreas is also removed regressive changes occur in the parathyroids and, moreover, these animals develop a decrease in blood serum calcium. This decrease can be prevented by injections of insulin. These studies confirm the known relation these three important functional units have to each other.

Two parathyroid tumors have been found at autopsies in patients with pituitary tumors; none have been removed during life. We found no evidence of pituitary tumors among reported cases of successful surgical

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removal of parathyroid tumors. Though there seems to be an association between adenomas of these two endocrine glands, the same has not been shown to be true for the adenomas of the pituitary body and the islands of Langerhans.

It is of interest to point out here that the first successful antemortem removal of parathyroid adenoma for the relief of the syndrome of hyperparathyroidism was accomplished by Mandl (5) in 1926. The syndrome of hyperinsulinism was described by Harris (2) in 1924 and Wilder *et al.* (6) in 1927 provided the final proof of the origin of hyperinsulinism as well as diabetes mellitus, when they found at operation an islet cell tumor in a patient with severe chronic hyperglycemia.

CASE REPORT

N.L.W. was a seaman first class, 26 years old, when admitted on July 7, 1942 to the sick list aboard ship. He complained of pain in the left flank and of passing blood in his urine during the previous five days. During this period he had passed a stone. He was transferred to a Mobile Hospital where roentgen studies revealed a small stone in the right renal pelvis and in the left upper ureter. On July 13, 1942, a left loin incision was made, and a calculus was removed from the left ureter. The next day he became irrational, but improved in the afternoon. Four days later he became semistuporous and developed a right hemiparesis and aphasia from which he recovered in about a week. The blood sugar was normal, as were all other studies, including the serum calcium. On August 1, 1942, he had another attack of hemiparesis and at this time the blood sugar was found to be 34.0 mg. per cent. He was given dextrose intravenously and quickly recovered. The diagnosis of adenoma of the islands of Langerhans was made. Frequent blood sugar determinations yielded values which varied from 41.0 mg. per cent to 59.0 mg. per cent. The blood sugar rose from 59.0 mg. per cent to 90.0 mg. per cent following the injection of adrenalin. On September 9, 1942, Lt. Comdr. Paul E. Spangler made a transverse incision of the abdomen, using spinal anaesthesia, and found three adenomas on the posterior surface of the tail of the pancreas; the adenomas measured 1.5 cm., 1.0 cm., and 0.5 cm. in diameter. These were removed. The patient's postoperative course was satisfactory, and following this his blood sugar remained above 100 mg. percent at all times.

On October 16, 1942, the glucose tolerance test was normal, but at this time, though ambulatory, he was not well. He complained of excessive salivation and frequent vomiting. X-ray showed that the right renal calculus was enlarging and extending into the calyces. The gastro-intestinal x-rays were normal. On October 16, 1942, a right pyelotomy was performed and the renal calculus removed. He was then transferred to the U. S. Naval Hospital at Oakland, California, and on his arrival on Nov. 12, 1942, the physical examination was negative except for the scars on his abdomen and a general unhealthy appearance. Roentgenograms revealed a recurrence of stones in the right renal pelvis and in the left ureter. At this time the diagnosis of hyperparathyroidism was suggested, and the blood calcium was found to be 13.5 mg. per cent and the urinary calcium excretion was indicated as three plus. He was still complaining of salivation, nausea and vomiting. An unsuccessful attempt was made to dissolve his renal stones by lavage with one per cent acetic acid solution. On December 9, 1942 it was noted that he had developed epigastric pain in addition to the other symptoms. He was listless, poorly nourished, and wan. He looked to be about five years older than his stated age. X-ray studies of his gastro-intestinal tract were repeated, and they revealed a duodenal ulcer. An x-ray film of the skull was made, and the following note was recorded: "Has a small pituitary tumor depressing the floor of the sella and eroding and spreading the clinoid processes laterally." The visual fields were normal. He was given full doses of deep x-ray therapy to the pituitary from December 11, 1942, until January 11, 1943, with no ill effect. He was also placed on a peptic ulcer regimen and his gastric symptoms cleared up.

In May, 1943, further x-rays of the skull indicated a slight but definite increase in the size of the pituitary tumor. There was no change in the degree of calcification of his bones. In June, 1943, he vomited blood on two occasions, but recovered with conservative treatment. At this time the serum calcium was 15.0 mg. per cent; the serum phosphorus was 5.7 mg. per cent; and the serum phosphatase was 3.1. Bodansky units. A severe alopecia had developed frontally and temporally corresponding to the areas radiated during the winter. It was noted that there had been a steady decline in pep and initiative. The skin was dry and old looking, and it was cold to the touch. The visual fields and fundi were normal. His renal stones were found to be increasing in size and he had stones in his bladder. The latter were crushed and removed. On August 9, 1943, he was still complaining of nausea and vomiting, never vomiting very much. Serum calcium was 15.0 mg. per cent and phosphorus was 8.3 mg. per cent. On August 21, 1943, he was transferred to a surgical ward for exploration of the parathyroid glands. However, this operation was not done. On December 11, 1943, at his own request, he was transferred to the U. S. Naval Hospital at Corpus Christi, Texas.

On admission to that hospital on December 15, 1943, the physical examination was negative except

that he appeared in poor health. His features were boyish, but he appeared more than 27 years of age. The skin was pale and dry; the hair was dry, and the nails brittle. He weighed 120 pounds, height 65 inches, and the blood pressure was 102/78. The vital signs were normal. No masses were felt in his neck and his thyroid was hardly palpable. The pubic hair was very fine and dry, but distribution was normal. He had a loss of libido. A glucose tolerance test was normal. This was fifteen months after the islet tumor had been removed. Blood calcium was 12.5 mg. per cent and the urinary calcium (Sulkowitch Method) was described as remarkably increased. On January 1, 1944, serum calcium was 13.7 mg. per cent and on January 17, it was 14.2 mg. per cent. Spinal fluid studies and urinalysis were normal.

It was very obvious that despite the fact that he had no palpable tumor in his neck he was suffering from hyperparathyroidism. X-ray showed very little demineralization of his bones. Exploration for tumor of the parathyroid gland was recommended by the medical service, and on March 1, 1944, the region of the thyroid gland was explored through a collar type of incision. The thyroid gland was small and firm. There was no parathyroid tissue visualized on the right side, but on the left side there was a small elongated mass of tissue behind the thyroid gland. Sections of this tissue were submitted to the National Naval Medical Center, where the diagnosis of benign adenoma of the parathyroid gland was made. The patient's blood calcium fell to 9.0 mg. per cent two days after the operation and has remained at that level. Frequent examinations of the urine since the day after the operation have shown normal calcium excretions.

Studies of his pituitary adenoma are in progress, and since he has had thorough x-ray therapy it may require years to complete these studies. In January, 1944, the visual fields showed a right temporal quadrant anopsia for form and red color. The left fields were normal. On April 1, 1944, the visual fields were found to be contracted in the upper outer temporal quadrant of only the right eye, indicating some improvement in the visual fields. X-ray films of the sella made at the U. S. Naval Hospital at Corpus Christi, Texas, have shown thickening of the floor of the sella turcica.

A complete re-examination of the patient during August, 1944, revealed that he had felt much better since the parathyroid operation, and had gained 15 pounds in weight, though he had had two attacks of peptic ulcer pain readily controlled by the Sippy regime. He was healthy in appearance. Gastro-intestinal x-rays showed persistence of the duodenal deformity. He had passed several renal stones, but stones were still present in the pelvis of each kidney despite efforts to dissolve them with citric acid solutions. They will be removed surgically. The right temporal quadrantal anopsia was still present.

SUMMARY

Dysinsulinism, hyperparathyroidism and a pituitary adenoma have been observed in the same patient. The presence of adenomas of the islands of Langerhans and of the parathyroid was proved by surgical excision. Their removal was followed by cure of these conditions. Removal of the pituitary tumor is not yet indicated. The diagnosis of this condition is based upon enlargement of the sella turcica and characteristic visual changes.

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LETTER FROM THE MANAGING EDITOR

The subscribers to this JOURNAL may be interested to know that the union of the May and June issues into one and the July and August issues into another has been undertaken as an expedient to catch up to date on publication. We recognize the necessity of meeting a publication date, but this has not been possible in the recent past because few manuscripts on original clinical research in endocrinology were submitted for publication. The reasons for the present scarcity of this type of material are not hard to find. It is believed that this "lean" period will continue for a time, yet there is every reason to expect a reversal of this trend. Many important studies already performed await release which has been withheld for security reasons, and a large group of well trained endocrinologists and clinicians are ready, as soon as conditions permit, to apply new techniques developed in experimental endocrinology. For many reasons, then, it seems best to retain the present method of publication, issuing a "thin" number, rather than making a change, such as, publishing on alternate months. Therefore, in the next few months we will present in each issue only a few articles, but the standards for the selection of material will be maintained. The subscriber will thus observe shorter and shorter "latent periods" in the appearance of each of these issues, until the dates of expected and actual appearance coincide, possibly in October. The publisher, Mr. Charles Thomas, will receive, we hope, fewer inquiries about missing numbers.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* F. A. DE LA BALZE, ISRAEL BRAM, CLARENCE D. DAVIS, ANNA FORBES, MURRAY B. GORDON, E. C. HAMBLEN, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO-MEMBRIVES, A. E. MEYER, E. C. REIFENSTEIN, JR., LEO T. SAMUELS, HAROLD WOOSTER, AND J. ZANARTU.

BOOK REVIEWS

J. C. MUSSIO FOURNIER, JOSÉ M. CERVIÑO AND JUAN J. BAZZANO

The Cardiovascular System in Thyroid Insufficiencies. Manuales de Medicina Práctica. Salvat Ed. Barcelona-Buenos Aires, 1944.

This monograph of 160 pages covers the field of cardiovascular symptoms in hypothyroidism rather completely. The various chapters deal with atheromatosis, the myxedematous heart, cardiac insufficiency, pathogenesis of the myxedematous heart and the various types of insufficiency, angina pectoris, and myxedematous dropsy. The extensive literature review is supplemented with the authors' own clinical cases, numerous electrocardiographs and radiographs. —*A.E.M.*

J. C. MUSSIO FOURNIER, RAÚL A. PIAGGIO BLANCO AND JOSÉ M. CERVIÑO

Skin and Its Derived Formations and Endocrine Glands. Manuales de Medicina Práctica. Salvat Ed. Barcelona-Buenos Aires, 1944.

According to the title, this monograph of 192 pages is restricted to the relationship between endocrine glands and skin, hair, nails, etc.; however, it includes many references to the general bodily shape and development as influenced by endocrine factors. The literature is covered extensively. Many illustrations from the authors' own experiences are presented. The skin disturbances in connection with disturbances of the thyroid, diabetes, the gonads, hypophysis, parathyroids, adrenals and thymus are discussed.—*A.E.M.*

ADRENALS

BLUMENTHAL, H. T.

An adrenal cortex stimulating substance in female human urine. *J. Lab. and Clin. Med.* 30: 428 (1945).

The presence of an adrenal cortex stimulating substance in the urine of normal and pregnant females was demonstrated by the effect of such urine on the mitotic activity within the adrenal cortex of immature female guinea pigs. With "normal female urine" the mitotic activity was 2.5 times that of the controls and almost exclusively noted in the outer half of the zona fasciculata. After the administration of "pregnancy urine" the mitoses were still greatest in the zona fasciculata, but as many as 15 per cent were also seen in the zona glomerulosa. Neither formalin nor thymol exerted any furthering or depressing action upon these effects of the urine. The author concluded that he was probably "dealing with a derivative of anterior pituitary substance or with some substance which acts in a similar manner."—*T.H.McG.*

GAUDINO, N. MARIO

The adrenals and nephrogenic hypertension. *Rev. Soc. Argent. de Biol.* 20: 470 (1945).

Bilateral adrenalectomy in normal rats produces a progressive descent in arterial pressure, in most of the cases down to subnormal values. Then, a great number of rats die after 30 days of the operation and the rest later normalize those values. In these adrenalectomized animals, treatment with adequate dose of desoxycorticosterone acetate normalizes the lowered pressure, an effect that disappears with the cessation of injections. In normal rats with intact adrenal glands, a daily dose of 2.5 mg. during seven days has practically no effect on arterial pressure. Unilateral adrenalectomy previous to the wrapping of the kidney with gauze and col-

lodion does not prevent the later development of hypertension; done after hypertension has settled in, it does not produce important variations on the pressure. Bilateral adrenalectomy on rats made hypertensive by renal wrapping causes the rapid fall of arterial pressure to a level equal to or lower than normal, between 3 and 8 days after the operation. When a group of animals die, another group maintains indefinitely their pressure at those values and the majority slowly redevelop hypertension, coinciding with the development of an accessory adrenal gland formed exclusively of cortical tissue. Treatment with desoxycorticosterone or 17-hydroxy-11-dehydrocorticosterone in hypertensive adrenalectomized rats re-establishes hypertension, in certain cases up to the levels existing prior to the extirpation. In that sense, the second of these substances seems more active. Cortical adrenal extracts have, with the dose used, in the same cases, a slight effect or none. Desoxycorticosterone acetate in hypertensive rats with intact adrenal glands does not modify the arterial pressure. Therefore, the presence of adrenal cortical tissue or of one or more of its hormones (desoxycorticosterone or 17-hydroxy-11-dehydrocorticosterone) seems necessary for the existence of renal hypertension and for the maintenance of normal arterial pressure.—*Author's Summary.*

RAPELA, CARLOS E.

Influence of adrenal extirpation upon the thymus. *Rev. Soc. Argent. de Biol.* 20: 439 (1945).

Adrenalectomy in male and female rats produced an increase in the weight and a true hyperplasia of the thymus. In both sexes adrenalectomy at an age of approximately 100 days produced the greatest increase in about 30 days after operation. Subsequent hypertrophy of the accessory adrenals, made up exclusively of cortical tissue, produced atrophy of the thymus. A few observations indicated that adrenalectomy produced a greater hypertrophy of the thymus in the female; but data were not conclusive. Results obtained confirm the observations of those who maintain that castration produces hypertrophy of the thymus. The effects of adrenalectomy and castration summate and hypertrophy was greater after the double operation than after removal of either gland separately. Thyroidectomy was followed by atrophy of the thymus. The opposite effects of the adrenals and the thyroid were independent of each other. Adrenal activity on the thymus was not dependent on the gonads or the thyroid. Hypophysectomy and adrenalectomy in the same animal produced such marked cachexia that it was not possible to establish whether the effect on the weight of thymus was due to removal of the glands or principally to the general metabolic disturbance.—*Author's Summary.*

SCHOLTZ, D. E., J. H. SCHULTZ, F. G. PLEUNE, K. FINK, L. T. STEADMAN, AND S. L. WARREN

Study of the body temperature and water content in shock produced by the continuous intravenous injection of adrenalin, with and without anesthesia. *J. Clin. Invest.* 24: 154 (1945).

The influence of continuous infusion of adrenalin at the rate of 0.010 mg. per kg. per minute for one hour has been observed under controlled conditions in young healthy dogs weighing from 9 to 28 kg. Adrenalin shock was accompanied by a fall in the temperature of peripheral muscles, but no change in the rectal readings. The application of heat to the four extremities did not have a beneficial effect. There was an initial rise in blood pressure followed by a steady fall until the animals expired. A rather rapid elevation of the hematocrit reading usually occurred following the beginning of the adrenalin infusion, which reached 120 per cent of the initial figure within a few minutes. The authors did not believe this was directly related to shifts of body water, as even the late effects of adrenalin shock showed no significant variations in total water balance. However, the kidneys and muscles of the chest did have a significant decrease in water content, while the heart and pericardial sac were the only structures in which an appreciable gain in water was observed. Nembutal anesthesia apparently aggravated the disturbances observed in adrenalin shock.—*T.H.McG.*

WOOLLEY, G. W. AND C. C. LITTLE

The incidence of adrenal cortical carcinoma in gonadectomized female mice of the extreme dilution strain. I. Observations on the adrenal cortex. *Cancer Research* 5: 193–202 (1945).

WOOLLEY, G. W. AND C. C. LITTLE

The incidence of adrenal cortical carcinoma in gonadectomized female mice of the extreme dilution strain. II. Observations on the accessory sex organs. *Cancer Research* 5: 203–210 (1945).

WOOLLEY, G. W. AND C. C. LITTLE

The incidence of adrenal cortical carcinoma in gonadectomized male mice of the extreme dilution strain. *Cancer Research* 5: 211–219 (1945).

Adrenal cortical carcinomas occurred in 100 per cent of 21 female mice of the ce strain 6–12 months following ovariectomy shortly after birth. No carcinoma occurred in unoperated controls. Growth and development of accessory sex organs followed the appearance of adrenal tumors attributable to estrogenic and androgenic effects from the cortical tumor. In male mice, castrated at 1–3 days of age, cortical tumors occurred in 15 of 19 animals, none in intact controls. Conditions in accessory sex organs indicated that castrated mice were being subjected to both estrogenic and androgenic influences of cortical origin in variable proportion.—*D.A.M.*

ENDOCRINE GENERAL

BIASOTTI, A., A. PATALANO AND R. E. MANCINI

Histological and physiopathological considerations in a case of renal diabetes. *Medecina* (Buenos Aires) 4: 297. 1944.

In a case of renal diabetes with marked glycosuria the authors studied: 1) the maximal tubular reabsorption of glucose and the excretion of diodrast, and 2) the histological appearance of renal tissue removed at biopsy. They found that the maximal ability to resorb glucose was decreased to 196.1 mg. per minute, and that the excretion of diodrast was also decreased to 22.4 and 30.2 mg. of iodine per minute. The glomerular filtration rate and the renal blood flow were normal. Histologically the general structure was essentially normal, but in several sections some of the tubules in the distal portion of the nephron showed an increase in the internal diameter and a flattening of the epithelium. Three methods were employed to study the glycogen content of the renal biopsy tissue, and all gave positive results. The glycogen was more abundant in the distal and the collecting tubules. The authors conclude that there is a decrease in tubular function in renal diabetes.—*F.A. de la B.*

BLOTNER, H.

Effect of prolonged physical inactivity on tolerance of sugar. *Arch. Int. Med.* 75: 39 (1945).

A study was made of prolonged physical inactivity on the dextrose tolerance of 86 non-diabetic patients—70 adults and 16 children—who had been confined to bed for 1 month to 13 years by various pathologic conditions. A comparison was made between the dextrose tolerance of these patients and that of active adults and children. The sugar tolerance was diminished in the patients bedfast for considerable periods. The fasting blood sugar ranged from 70 to 130 mg. per 100 cc., and the fasting urine was free from sugar. After ingestion of dextrose the concentration of blood sugar rose to abnormal levels (maximum 364 mg.) and varying amounts of sugar were found in the urine at various times. In some patients who later became ambulatory for several months the sugar tolerance returned to normal. Age appeared to have no definite relation to the diminished sugar tolerance. Hypertension, vascular disease, obesity and infection in themselves did not appear to be significant as causes. The arteriovenous differences in the blood sugar of a group of inactive patients after the ingestion of dextrose ranged from 15 to 50 mg. per 100 cc., which is normal or greater than normal. Hence the muscles of the physically inactive patients are capable of utilizing sugar normally. It is suggested that during prolonged physical inactivity the pancreas is at rest because in this state there is not the demand for rapid storage and utilization of sugar that there is in active persons. In consequence, there may ensue diabetic-like reactions to dextrose tolerance tests even with normal fasting levels of blood sugar.—*Author's Summary.*

DEL CASTILLO, E. B., F. A. DE LA BALZE AND J. REFORZO-MEMBRIVES

Gynecomastia and cancer of the lung. *Medecina* (Buenos Aires) 4: 176 (1944).

The authors describe a male patient with bronchopulmonary carcinoma and gynecomastia; the same authors have reported three other patients with the same syndrome in 1941. All of these patients showed pronounced chronic pul-

monary osteoarthropathy. In the present case a number of studies were made: 1) the urinary excretion of estrogens as determined by the Allen and Doisy test was found to be increased to 40 rat units per 24 hours; 2) five determinations of the urinary 17-ketosteroid excretion on different occasions were somewhat below normal and averaged 9.5 mg. of steroid per 24 hours; and 3) the Freidman test was negative, indicating that excessive amounts of chorionic gonadotrophin were not excreted. Biopsy of the testis was not done, but as far as possible other causes of gynecomastia were excluded. The authors believe that the gynecomastia in this syndrome is due either to an increase in the circulating estrogens or to an alteration in the normal androgen-estrogen relationship. The mechanism by which increased estrogen affects the breast is discussed. The authors postulate a predisposing factor in the glandular tissue of the breast.—*F.A. de la B.*

COWIE, A. T.

Fracture of the Pelvic Bones in Bovines Implanted With Tablets of Synthetic Oestrogens. *J. Endocrinol.* 4: 19. 1944.

Trauma from persistent coital mimicry was responsible for the fractures with the changes in pelvic morphology as a probably predisposing factor. There was no evidence of bone rarefaction.—*L.T.S.*

DARLEY, W., R. W. GORDON, AND K. T. NEUBERGER

Simmonds' disease with therapeutic response to hormone therapy for four years: Report of a case with necropsy findings. *Ann. Int. Med.* 21: 890–902. 1944.

A 21 year old man who was treated for syphilis, developed a typical case of Simmonds' disease after an attack of severe influenza. Thyroid treatment had no effect on the endocrine condition for the next 23 years. An improvement in general symptoms but not in sexual power or hair growth was noted in the following four years on the administration of chorionic gonadotropic hormone.

The patient died. Necropsy revealed complete obliteration of the pituitary, marked sclerosis of the thyroid and testes and atrophy of the prostate and adrenal, together with moderate degenerative changes in the brain particularly in the thalami and the interbrain. No manifestation of syphilis was found. The authors feel that this was a case of Simmonds' disease (primary atrophy of the pituitary) and not Falta's disease (pleuriglandular sclerosis).—*M.B.G.*

EDMONDS, H. W.

A nomogram for organ weights of children. *J. Lab. and Clin. Med.* 29: 1300. 1944.

The author has adapted the figures of Coppoletta and Wolbach or the average weights of the various organs to the production of a graphic representation of these on a dial. This can be superimposed upon the dollars and cents scale of the ordinary commercial platter-type fan-dial springless balance in such a way that the actual weight of the tissue is compared with the theoretical norm for the particular age group. This may prove to be a helpful adjunct in the analyzing post mortem data from patients with endocrine disease.—*T.H.McG.*

ELLIS, ALBERT

The sexual psychology of human hermaphrodites. *Psychosomatic Med.* 7: 108. 1945.

Eighty-four cases of hermaphroditism from the medical literature are examined, and it is shown that, in the gerat majority of these, the hermaphrodite assumes a heterosexual libido and sex role that accords primarily not with his or her internal and external somatic characteristics, but rather with his or her masculine or feminine upbringing. This is shown to be true in the case of pseudohermaphrodites, presumably true hermaphrodites, and true hermaphrodites. On the basis of these facts, the conclusion is drawn that heterosexuality and homosexuality in hermaphrodites are primarily caused not by direct hormonal or other physiological factors but by environmental ones. Since, however, the hermaphrodites' environment conspicuously includes his somatic anomalies, it is also concluded that the problem of "normal" and "abnormal" sexual behavior among hermaphrodites is importantly a psychosomatic one, as is, too, the broad problem of psychosexuality in normal human beings.—*Author's Summary.*

FIELDS, H.

The Influence of Stilbestrol upon Lactation. *Am. J. Obst. and Gynec.* 49: 385. 1945.

The effect of diethylstilbestrol upon lactation in a series of 250 patients was observed in 4 groups under the following conditions: in the ab-

sence of nursing, no pumping of the breasts; in the absence of nursing, with pumping of the breasts; following short period of nursing; and during nursing. Routine treatment for each group was as follows: fluid intake at least 3000 cc. every 24 hours; no unusual cathartics; support of breasts, no tight binders; and diethylstilbestrol, 1 mg. three times daily for five days. The author concludes that: diethylstilbestrol is effective in aiding cessation of lactation; given to normally nursing postpartum women, it will depress milk secretion in spite of normal suckling; in rare cases, diethylstilbestrol may have no obvious effect upon lactation; and the dosage bears no quantitative relation to its effectiveness in depressing milk secretion.—*C.D.D.*

FOLLEY, S. J., AND F. H. MALPRESS

The artificial induction of lactation in the bovine by the subcutaneous implantation of synthetic oestrogen tablets. *J. Endocrinol.* 4: 1. 1944.

1. Lactation was induced in nulliparous heifers and dry cows by the subcutaneous implantation of large numbers of small tablets of diethylstilbestrol or hexoestrol. Individual variation in response was large, but in some cases the lactation curve was comparable with that of normal lactation. The best response was obtained with a dry cow which gave a maximum yield of 30½ lb. daily and a total yield of 7400 lb. Implants totalling 5.0 and 2.5 g. were equally effective, and there appeared to be no difference in efficacy between diethylstilbestrol and hexestrol. Copious lactation was also induced in nulliparous heifers and dry cows by the subcutaneous implantation of one or two tablets of hexestrol weighing approximately 1000 mg. Estrogen treatment was, in most cases, accompanied by a nymphomaniac syndrome, which, in 20% of the experiments in which small tablets were implanted, culminated in pelvic fracture.—*L.T.S.*

FOLLEY, S. J., AND F. H. MALPRESS

Artificial induction of lactation of Bovines by oral administration of synthetic oestrogens. *J. Endocrinol.* 4: 23. 1944.

A preliminary experiment in which eight heifers were given daily doses of hexestrol or dienestrol in their food or drinking water indicated that lactation could be satisfactorily induced in this way. A further experiment involving thirty-two heifers, in which diethylstilbestrol or dienestrol was fed daily, gave less encouraging results, only nineteen of the animals being brought into lactation and the general plane of response being markedly lower. Variability of the response in all its quantitative aspects was a feature of these experiments.

The yields generally were inferior to those given in the implantation experiments reported in the previous paper, and far more estrogen was needed to evoke response.

The general 'condition' (using the word 'condition' in the special sense in which it is used in animal husbandry) of the animals suffered in no way from the treatment, and nymphomaniac effects were not pronounced. No pelvic features were caused, but two serious cases of vaginal and rectal prolapse was encountered. Thirty of the animals used in the main experiment have since been served and twenty-five have become pregnant, in many cases to the first service.—*L.T.S.*

FOLLEY, S. J., AND F. H. MALPRESS

The chemical composition of bovine mammary secretions induced by the subcutaneous implantation or oral administration of synthetic oestrogens. *J. Endocrinol.* 4: 37. 1944.

The mammary excretions produced by heifers artificially brought into lactation by treatment with synthetic estrogens were at the outset colostral in nature, but the composition gradually changed to that characteristic of milk of good chemical quality at a rate roughly proportional to the rate of increase in yield.—*L.T.S.*

FOLLEY, S. J., D. L. STEWART, AND F. G. YOUNG

Experiments on the use of Tablets containing 50% hexoestrol for the artificial induction of lactation in the bovine. *J. Endocrinol.* 4: 43. 1944.

Experiments have been carried out on the use of subcutaneous implants of tablets containing 50% hexestrol, 49% lactose and 1% stearic acid for artificial induction of lactation in maiden heifers and dry cows. Individual variations in response were large, but satisfactory responses were given by two heifers and one dry cow to low total doses of estrogen. The responses of six heifers giving small amounts of secretion to further implants consisting of pure hexestrol tablets were also variable. In two cases marked increases in yield resulted. Symptoms of

nymphomania were observed in all animals but none suffered pelvic fracture. Of six animals retained for breeding after cessation of treatment, five became pregnant to the first mating. All delivered male calves, two being born dead and another prematurely. Under the conditions of these experiments tablets containing 50% hexestrol were absorbed more slowly than pure hexestrol tablets of comparable size.—*L.T.S.*

HEINBECKER, P.

The pathogenesis of Cushing's syndrome. *Medicine* 23: 225. 1944.

Clinical and experimental studies are reported. At least three primary lesions—adrenal cortex tumor, tumor of the thymus, or atrophy of the nuclei of the hypothalamus—are the probable precursors of the hyalinization of the basophile cells of the hypophysis. Sixteen references; six case reports.—*Courtesy Diabetes Abstracts.*

HUGHES, E. C.

Relationship of glycogen to problems of sterility and ovular life. *Am. J. Obst. and Gynec.* 49: 10. 1945.

The endometrium obtained by biopsy from normal cyclic women was studied for the presence of an enzyme responsible for glycogen hydrolysis. One hundred and forty-seven analyses were done on 50 women at varying times of the cycle. The average amounts of enzyme varied as follows: days 1 to 6—11.5, 7 to 15—15.6, 16 to 23—30.6, 24 to 26—30.9 and 26—36.9 mg. per gram. The distribution of glycogen in the endometrium as determined by Best carmine technique was normal in all these endometriums. Forty women who presented themselves for sterility studies were tested for enzyme concentration. Normal endometrial patterns for the twenty-sixth day of the cycle with normal distribution of glycogen was found 66 times. Seventeen of these women had enzyme determinations. The average was 30.5 mg. per gram, which is considered normal. The endometrium failed to proceed farther than the proliferative phase in 27 women. Enzyme determination in seven of these patients was under normal, averaging 16.4 mg. per gram. Treatment with various gonad-stimulating hormones was unsatisfactory. An early secretory endometrium was seen in 31 patients. In 16 other patients, the endometrium was spotty, in some areas progressing to early secretory, and in other portions to the late secretory phase. Both of these two groups had an irregular distribution of glycogen and the enzyme content was markedly below normal. On the basis of abortion statistics for the entire series, the authors believe that when the glycogen metabolism is not complete, the opportunities for ovum survival are not good.—*C.D.D.*

MCGAVACK, T. H., AND MILDRED VOGEL

Propylene glycol as a menstruum for the administration of steroid hormones. *J. Lab. and Clin. Med.* 29: 1256. 1944.

The very low toxicity of propylene glycol prompted a study of its use as a menstruum for the intravenous administration of the relatively water insoluble steroid hormones. Repeated daily injections of large amounts of propylene glycol had no measurable influence upon the health of dogs or human beings. Desoxycorticosterone acetate, 10 mg. per 1 cc. of propylene glycol was given intramuscularly and intravenously to both dogs and human beings. No ill effects were observed in 3 patients who received 1.5 cc. daily intravenously for periods of 12 successive days each. In dogs, no untoward clinical reactions were caused by single injections of desoxycorticosterone acetate in doses of 100 mg., representing 10 cc. of propylene glycol, whereas nausea and vomiting appeared if 200 mg. were similarly given. After repeated intravenous injections of such large doses into dogs acicular material could be found in the lungs at autopsy. However, animals receiving 100 mg. or less daily for periods up to 43 days showed no such deposits. Although embolic phenomena were carefully watched for in both dogs and human beings, no evidence of such complications were observed in either, nor could embolic areas be identified in any of the tissues of the dogs at the time of sacrifice. It is concluded that propylene glycol is a safe menstruum for the administration of desoxycorticosterone acetate in any known therapeutic range of dosage. Certain simple rules for the administration of the material are suggested.—*Author's Summary.*

NICODEMUS, R. E., AND L. F. RITMILLER

An analysis of sterility studies in the female. *Am. J. Obst. and Gynec.* 49: 95. 1945.

An analysis is presented of 76 instances of sterility in the female. Sixty-eight of the 71 husbands that were examined were reported as having an ample number of motile spermatozoa

with good morphologic characteristics. No detailed findings are given. The endocrine status of the wives were as follows: normal, 31.5%; hypothyroidism, 47.4%; pituitary "dysfunction," 6.6%; and ovarian "dysfunction," 14.5% Hysterosalpingograms were done on 21 women and seven had bilateral occlusion. Tubal insufflations were done on 45 patients and 17 had bilateral occlusion. Of the 76 studied and treated, a total of 29 pregnancies resulted, 26 of which went to term. The greatest number of pregnancies occurred in the hypothyroid and ovarian "dysfunction" group that received thyroid extract, estrogenic therapy and/or follicular stimulating hormone.—*C.D.D.*

PRUDENTE, A.

Postoperative prophylaxis of recurrent mammary cancer with testosterone propionate. *Surg., Gyn., & Obst.* 80: 575–92. 1945.

Therapeutic results obtained in treating 64 cases of cancer of the breast by radical surgery between 1932 and 1939 have been compared with those obtained in treating 63 similar cases since 1939 with testosterone propionate after radical surgery. As gauged by the survival rate after 3, 4 or 5 years there is almost 100% improvement in the results for the group treated with testosterone and surgery, as compared with the group subjected to surgery alone. In planning the dosage of testosterone, the following factors were taken into consideration: (1) histologic grade of malignancy, (2) clinical stage, (3) age, (4) menstrual cycle, (5) biotype. Patients with the highest grades of malignancy should be given a massive dose of 175 mg. per week, regardless of age. The author recommends that treatment be continued for 5 years with gradual reduction of dosage. Signs of virilization occurred almost exclusively in young women in whom the weekly dose was above 30 mg. and total dose 800–1500 mg. of testosterone propionate. Menstrual irregularities were the rule. In women over 40, the onset of the menopause was greatly hastened. Testosterone propionate appears to exercise a protective or prophylactic action against recurrences of surgically treated mammary cancer.—*J.M.*

SHARPEY-SCHAFER, E. P.

Endocrinology. *Practitioner* 153: 302. 1944.

Except thyrotoxicosis, diabetes mellitus and sex gland deficiency in women, demonstrable disease of the endocrine glands is uncommon. The author's point of view in regard to the efficacy of endocrine therapy is somewhat pessimistic. He thinks that the therapeutic value of many glandular products has been over-rated. His estimates are as follows: (1) Pituitary: extracts disappointing; of some use in dwarfism; of questionable value in stimulating lactation; of no effect on carbohydrate metabolism; anorexia nervosa may be due to functional pituitary deficiency. (2) Thyroid: essential in cretinism and myxedema; valuable in partial thyroid deficiency; thiourea and thiouracil effective in thyrotoxicosis. (3) Sex glands: the sex hormones are classed and listed as those which give good results in most cases, good results in a few cases, and doubtful or no results; in the first class he recognizes only androgens for deficiency in males, estrogens for deficiency in females and estrogens for satyriasis in males. Under the 2nd class 7 types of therapy are included, namely for cryptorchidism, anovulatory cycles, male climacteric, dysmenorrhea, premenstrual disorders, prostatic carcinoma, inhibition of lactation. Six common types of sex gland therapy are noted under the last class. (4) Adrenal: the value of desoxycorticosterone acetate (DCA) is discussed.—*Courtesy Biol. Absts.*

SHELDON, D. E.

Pregnancy complicated by Addison's disease. *Am. J. Obst. and Gynec.* 49: 268. 1945.

A case report is presented of a normal parturition and puerperium in a 28 year old primigravida in whom a clinical diagnosis of Addison's disease was made. The patient was treated with high protein, high carbohydrate, high salt and low potassium diet, added salt and adequate adrenal cortical extract. The author does not believe that pregnancy has affected the course of the disease to date.—*C.D.D.*

STODDARD, F. J.

Hirsutism in Pregnancy. *Am. J. Obst. and Gynec.* 49: 417. 1945.

Two instances of marked hirsutism in pregnancy are reported. In the absence of definitely demonstrable neoplasm by clinical, laboratory or x-ray studies, exploratory laparotomy offers little. The hirsutism will in all likelihood disappear during the postpartum period, but will probably return with subsequent pregnancies. There is no indication here for termination of pregnancy. In one instance reported here, the

17-ketosteroids were 12.0 and 8.2 mg. per 24 hours, the comparable normal for pregnancy being 3 to 6.5 mg. Some 10 weeks after delivery, the 17-ketosteroids were 3.4 mg. per 24 hours, the comparable normal nonpregnant range being 1.5 to 8.5 mg. with an average of 5.3 mg. per 24 hours.—*C.D.D.*

TOMLINSON, W. J.

Cortical necrosis of kidneys associated with necrosis of pituitary in obstetrical shock. *Am. J. Obst. and Gynec.* 49: 236 (1945).

The author presents a detailed case report of the combined necrosis of the anterior lobe of the pituitary gland and the cortices of the kidneys following severe obstetrical shock which followed the mid-forceps extraction of a term stillborn child and the manual removal of the placenta. The estimated blood loss did not exceed 300 cc. The patient was anuric following this and died six days later. There were no signs of eclampsia and no autopsy evidence of the usual toxemias of pregnancy. The author could find no similar case reported in the literature.—*C.D.D.*

WILKINS, L., AND W. FLEISCHMANN

Studies on the creatinuria due to methylated steroids. *J. Clin. Invest.* 24: 21 (1945).

Observations were made on sexually undeveloped dwarfs between the ages of 11 and 22 years, who received diets of constant carbohydrate, protein and fat content, furnishing less than 30 mg. of creatine daily. In 11 subjects receiving 25 mg. of methyl testosterone daily there was a latent period of from four to 16 days during which creatine and creatinine excretion occurred during the remainder of the first month and a steady rise continued thereafter until the third to sixth months. After this, relatively constant levels were maintained as long as the administration of methyl testosterone was continued. The changes in creatinine excretion were similar in direction but much less pronounced than were those of creatine. Indeed, before treatment the ratio of creatine to creatinine was approximately 1 to 14.5 whereas under treatment the output of the former approached that of the latter and, in some instances between the third and sixth months, exceeded it. On withdrawing the drug, irrespective of the length of treatment, there was usually, although not always, a temporary increase in the creatinuria and creatininuria which reached its peak in from 4 to 14 days, followed by a relatively rapid drop in these values to the pretreatment levels. Testosterone proprionate in doses of 25 mg. daily intramuscularly produced a decrease in creatine excretion which was maintained during periods of treatment up to 2 months. After it was discontinued there occurred a transient rise in the excretion of both creatine and creatinine similar to that noted with methyl testosterone. After 36 days of treatment with methyl testosterone a patient was given, in addition, testosterone propionate daily for 14 days without any appreciable influence on the creatinuria and creatininuria produced by the methyl testosterone. When methyl testosterone was given intramuscularly its action was identical with that obtained by oral administration. Hypothyroid patients responded to methyl testosterone in a manner similar to normal individuals. The authors believe that the creatinuria produced by methyl testosterone is due to an increased synthesis of creatine. They further conclude that both methyl testosterone and testosterone propionate increase the amount of creatine stored in the muscles. The differences between the creatinuria induced by the ingestion of methyl testosterone and that caused by feeding desiccated thyroid substance to hypothyroid children are noted; viz, that in the latter, there is a sharp increase in the excretion of creatine during the first 2 to 3 days of treatment without a latent period or initial decrease. Moreover, the peak of excretion is reached between the 10th and 30th days, with a subsequent gradual decline to the range encountered in normal children. It is suggested that the ability of methyl testosterone to increase creatine production and the failure of testosterone propionate to do so is related to the different manner in which the 17-methylated and nonmethylated compounds are catabolized. In this connection, twelve steroid compounds were studied for their ability to produce creatinuria: androsterone; dehydroisoandrosterone acetate; androstenedione (3, 17); testosterone; testosterone propionate; Δ_5 androstenediol (3β, 17α); Δ_5 androstenediol (3β, 17α) diacetate (3, 17); androstenediol-(3α, 17α)-diacetate (3, 17); methyl testosterone; 17-methyl androstene-diol (3β, 17α); 17-methyl Δ_5 androstenediol (3β, 17α); 17-Methyl androstenediol-3 (α), 17 (α); and 17-ethyl testosterone. Creatinuria occurred only in association with the administration of the three of these that had a methyl radical attached at carbon atom 17.—*T.H.McG.*

THYROID

BRIGNONE, REINALDO F.

Modifications of carbohydrate metabolism in hyperthyroidism. (Modificaciones del metabolismo de los hidratos de carbono en el hipertiroidismo.) *Rev. Soc. Argentina Biol.* 20: 260 (1944).

Mild hyperglycemia up to 149 mg.% was observed in 31 dogs treated with thyroid substance in doses of 0.5 to 4 gm. per kg. daily. Larger doses caused further increase in the blood sugar, although no regular relationship was found between treatment and effect. With prolongation of treatment for 14–16 days the blood sugar fell again. Diabetes never occurred. Hyperglycemia induced by oral administration of galactose reached a maximum earlier in dogs treated with thyroid than in normal dogs; the same was observed after intravenous injection of galactose but only after thyroid treatment for eight to 16 days. Glycogen reserves decrease in thyroid treated dogs, especially liver glycogen. The glycogen in the heart and striated muscles diminishes only after longer treatment. The oral administration of galactose to hyperthyroid patients produces a more rapid and greater increase in blood sugar than in normal persons.—*A.E.M.*

LEWIS, L. A., AND E. P. MCCULLAGH

Electrophoretic analysis of plasma proteins in hyperthyroidism and hypothyroidism. *Am. J. Med. Sci.* 208: 727 (1944).

The plasma proteins of 14 hyperthyroid and six hypothyroid patients were studied by the Tiselius electrophoresis method. Control values were established on 21 normal subjects. In the hyperthyroid cases the plasma albumin was below normal levels both in grams per 100 cc. and in percentage of total plasma protein. In the majority of the cases the alpha globulin was markedly increased. No consistent change was observed in the other globulin fractions. After thyroidectomy, when all symptoms of hyperthyroidism had subsided, the plasma protein picture was normal or had values only slightly beyond the normal range. In patients with progressive exophthalmos and no other residual symptoms of Graves' disease, there was a low plasma albumin but no consistent change in the globulin fractions. In the hypothyroid cases there were a low plasma albumin, a low alpha globulin and an increased beta globulin. After some months of thyroid therapy the plasma protein picture approximated the normal. The authors suggest that: (1) the decreased albumin in hyperthyroid patients may be due to impaired liver function or hepatic damage; (2) since vitamin B complex delays the onset of liver derangement in hyperthyroid dogs, the patients with the greatest alterations in plasma proteins were probably receiving the least adequate vitamin B complex diet (this is difficult to prove since hyperthyroidism has usually been present for some time before the first studies can be made); (3) the return of the plasma protein levels to normal after abatement of hyperthyroid symptoms could be explained by reversible liver changes; and (4) since the beta globulin in the hypothyroid cases was most elevated when the plasma cholesterol was high, there may be a combination between lipids and beta globulin as postulated by Abramson and co-workers.—*E.C.R., Jr.*

LIPTON, R. F., AND M. S. ABEL

Aspiration biopsy of the thyroid in the evaluation of thyroid dysfunction. *Am. J. Med. Sci.* 208: 736 (1944).

The authors have devised a method for obtaining aspiration biopsies of the thyroid gland which is simple and thus far safe. With this method they compared aspiration specimens with regular pathologic specimens of the removed glands from the 17 patients who were subsequently operated on for hyperthyroidism. The diagnosis of toxicity was made in 16 of the cases from the aspiration specimens alone using the mean acinar cell height of 100 cells. The mean cell heights also agreed very closely with those obtained from the routine surgical sections. The diagnosis of toxicity correlated with the clinical status of the patients. Aspiration biopsy of three normal glands gave sections with mean cell heights consistent with normal glands. The standards for acinar cell height employed by the authors include: (1) an average cell height of over 8.1 microns for toxicity in nodular goiters, (2) an average cell height of over 7 microns for toxicity in diffuse goiters, and (3) an average cell height of under 7 microns for a normal gland. The authors suggest that this direct method may prove to be a valuable adjunct in the diagnosis of thyrotoxicosis.—*E.C.R., Jr.*

MONASTIKSKY, S. M.

Treatment of congenital hernia with desiccated thyroid gland. *Semana méd.* 51: II: 831 (1944).

A two months old male child had a right inguinal hernia of three cm. diameter with threatened strangulation, a left inguinal and an umbilical hernia. The right hernia was bandaged and thyroid medication given, although the child did not seem to be a hypothyroid case. The features, however, were mildly, although not typical, cretinoid. The parents were alcoholics. After 40 days the left inguinal and the umbilical hernia had disappeared, the right was reduced to 1.5 cm. in diameter. Six months later this hernia had disappeared. Three similar cures were obtained in other children.—*A.E.M.*

MOSCHCOWITZ, E., AND S. S. BERNSTEIN

The relation of neurocirculatory asthenia to Graves' disease. *Am. Heart J.* 28: 177 (1944).

All evidences point to the psychosomatic nature of neurocirculatory asthenia. Neurocirculatory asthenia is by no means a disease incidental to war, and it is more common in women than men. Viewed from the dynamic and biologic aspects of Graves' syndrome, the similarity between neurocirculatory asthenia and the initial or larval phase of Graves' syndrome is so close that it is believed that the two are identical. Transitions of neurocirculatory asthenia to Graves' syndrome and the reverse are by no means uncommon. Eleven such instances are reported.—*Authors' Abstract.*

ROSE, E., AND J. MCCONNELL

Thiouracil in the treatment of thyrotoxicosis. Clinical experience with 37 cases. *Am. J. Med. Sci.* 208: 561 (1944).

The authors summarize their experience at the University of Pennsylvania Hospital as follows: (1) Thirty patients (81%) showed a favorable response, four (10.9%) showed a partial response and two (5.4%) showed no response to treatment. Associated conditions may have influenced the reaction of three of the six patients with an unsatisfactory response. (2) In four patients thiouracil was used during preparation for thyroidectomy. One of these died 20 hours after operation, but thiouracil was not regarded as a factor in his death. (3) The control of thyrotoxicosis with thiouracil in a 13 year old girl with diabetes mellitus was not followed by a change in either carbohydrate-tolerance or insulin requirement. (4) As reported by others, the glands removed after thiouracil treatment showed hyperplasia on histological study. (5) Eight patients had remissions lasting (at the time of communication) for three weeks to seven months after withdrawal of thiouracil, and three patients had a similar response when placed on minimal doses (0.1 to 0.2 gm. daily); in contrast, 13 patients relapsed when thiouracil was reduced in dosage or withdrawn, but all of them responded again to re-administration of thiouracil. (6) Under thiouracil therapy, the reduction in cardiac output (measured by ballistocardiogram) of nine patients paralleled the decline in basal metabolic rate. (7) No evidence of refractoriness to thiouracil was observed. (8) Untoward reactions attributable to the drug occurred in eight patients. The most important of these were neutropenia with pharyngitis and fever, noted in two cases. Reduction in the size of the thyroid gland was observed in eight patients after prolonged treatment. Exophthalmos tended either to remain stationary or to increase slightly. The authors conclude that while further work remains to be done before the clinical usefulness of thiouracil can be finally evaluated, the drug effectively controls most of the phenomena of thyrotoxicosis in the majority of patients, and, hence, its use at present is justified in the protracted treatment of mild or moderately severe cases and in the preparation of selected patients for thyroidectomy. It may also prove to be of considerable value in patients regarded as unacceptable surgical risks.—*E.C.R., Jr.*

WILLIAMS, R. H.

Antithyroid drugs, with particular reference to thiouracil. *Arch. Int. Med.* 74: 479 (1944).

This is an excellent summary of the subject and should be studied in the original to be fully appreciated. In the last few years a great deal of progress has been made in elucidating the physiology of the thyroid gland and in establishing some of the relationships of its function to the pituitary gland and the body cells. As a result of this progress thyrotoxicosis is treated with greater effectiveness. The drugs which

have been of greatest aid are iodine, cyanides, thiocyanates, sulfonamide compounds, and thioureas. Since these substances inhibit the function of the thyroid gland, they are spoken of as antithyroid drugs. This is true in spite of the fact that they may increase the work of the gland, as evidenced by the marked hyperplasia and hypertrophy which they produce in the thyroid. Many of the antithyroid substances discussed have been of great aid in illustrating the integrative nature of the pituitary-thyroid-body cell relationships as well as in leading to a better understanding of the intrinsic physiology of each unit. Although many of the claims for iodide therapy remain in dispute, there is general agreement as to its major effects. The effectiveness of radioactive iodine in the treatment of thyrotoxicosis remains an unsettled question. Indications are that thiouracil is superior to any other form of therapy utilized thus far in producing and maintaining a remission of thyrotoxicosis. Early fears of the goitrogenic effects of thiouracil seriously handicapping its use are no longer justified. Whereas it sometimes causes further enlargement of the thyroid gland, for the most part a reduction in size results after prolonged therapy. Although the technical difficulties of thyroidectomy are greater in some cases in which the patients are prepared with thiouracil than in comparable ones in which they are prepared with iodide, these are reduced by using iodide or desiccated thyroid in conjunction with thiouracil. It is too early to state how extensively thiouracil therapy should be used to the exclusion of subtotal thyroidectomy. Except in a few cases in which there are toxic reactions to thiouracil, the drug can be used indefinitely and that as long as it is used a remission of the disease is maintained. However, the obscurity of the primary cause of the disease makes it difficult to know what the ultimate goal in treatment should be, other than to abolish the obvious manifestations of the disease. The effectiveness of thiouracil in the treatment of thyrotoxicosis is apparently due to its inhibition of the manufacture of the thyroid hormone. The hormone already manufactured will in time become broken down, and a remission of the thyrotoxicosis will then ensue, but the evidence suggests that the pituitary may become even more active, and as a result hyperplasia of the thyroid gland persists or actually increases. However, since in a few patients thyrotoxicosis has been shown to remain in remission for several months after discontinuance of thiouracil therapy, certain changes must take place under the influence of thiouracil in the pituitary or thyroid or some other portion of the body which interfere with the manufacture or stability of the hormones or with the capacity of the end organs to respond. The only really serious toxic reaction reported thus far has been agranulocytosis, which has occurred in only in one per cent of the cases. It seems probable that with the precipitously rising tide of interest in this line of investigation either a substance related to thiouracil or perhaps one of an entirely different basic structure with undisputed therapeutic superiority will evolve, as has been the story with the antibacterial drugs.—*I.B.*